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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 11 Nov 2003 (20031111/PD)
FILE LAST UPDATED: 11 Nov 2003 (20031111/ED)
HIGHEST GRANTED PATENT NUMBER: US6647548
HIGHEST APPLICATION PUBLICATION NUMBER: US2003208825
CA INDEXING IS CURRENT THROUGH 11 Nov 2003 (20031111/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 11 Nov 2003 (20031111/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2003
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=> s arthritis and sulfonylaminocarbonyl
         31792 ARTHRITIS
           111 SULFONYLAMINOCARBONYL
L1          28 ARTHRITIS AND SULFONYLAMINOCARBONYL

=> s l1 and pd<2001
       2781385 PD<2001
                  (PD<20010000)
L2          21 L1 AND PD<2001

=> d l2 1-21

L2   ANSWER 1 OF 21  USPATFULL on STN
AN     2000:9876  USPATFULL
TI     Peptide, peptide analog and amino acid analog protease inhibitors
IN     Munoz, Benito, San Diego, CA, United States
       McDonald, Ian A., San Diego, CA, United States
       Albrecht, Elisabeth, San Diego, CA, United States
PA     Sibia Neurosciences, Inc., La Jolla, CA, United States (U.S.
       corporation)
PI     US 6017887              20000125                              <--
AI     US 1995-443931          19950518 (8)
RLI    Continuation of Ser. No. US 1995-403420, filed on 13 Mar 1995 which is a
       continuation-in-part of Ser. No. US 1995-369422, filed on 6 Jan 1995,
       now patented, Pat. No. US 5804560
DT     Utility
FS     Granted
LN.CNT 3617
INCL   INCLM: 514/019.000
       INCLS: 562/575.000; 570/123.000; 514/724.000
```

NCL NCLM: 514/019.000
NCLS: 514/724.000; 562/575.000; 570/123.000
IC [6]
ICM: A61K038-05
EXF 514/18; 514/19; 562/575; 530/331
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 2 OF 21 USPATFULL on STN
AN 1999:170588 USPATFULL
TI Perfluoroalkyl ketone inhibitors of elastase and processes for making the same
IN Curran, Timothy T., Chester, NY, United States
Burkhart, Joseph P., Plainfield, IN, United States
Angelastro, Michael R., Mason, OH, United States
Peet, Norton P., Cincinnati, OH, United States
Metz, Jr., William A., Loveland, OH, United States
PA Hoechst Marion Roussel, Inc., Bridgewater, NJ, United States (U.S. corporation)
PI US 6008196 19991228 <--
WO 9533762 19951214 <--
AI US 1996-737905 19961122 (8)
WO 1995-US5363 19950501
19961122 PCT 371 date
19961122 PCT 102(e) date
RLI Continuation of Ser. No. US 1994-327520, filed on 20 Oct 1994, now patented, Pat. No. US 5403052 which is a continuation-in-part of Ser. No. US 1994-252857, filed on 2 Jun 1994, now abandoned
DT Utility
FS Granted
LN.CNT 1792
INCL INCLM: 514/018.000
INCLS: 530/330.000; 530/331.000
NCL NCLM: 514/018.000
NCLS: 530/330.000; 530/331.000
IC [6]
ICM: A61K038-06
ICS: A61K038-07; C07K005-08; C07K005-10
EXF 530/330-331; 514/18
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 3 OF 21 USPATFULL on STN
AN 1999:132782 USPATFULL
TI Acylated enol derivatives as prodrugs of elastase inhibitors
IN Peet, Norton P., Cincinnati, OH, United States
Burkhart, Joseph P., West Chester, OH, United States
Mehdi, Shujaath, West Chester, OH, United States
PA Merrell Pharmaceuticals Inc., Bridgewater, NJ, United States (U.S. corporation)
PI US 5972897 19991026 <--
AI US 1997-882764 19970626 (8)
RLI Division of Ser. No. US 1996-670136, filed on 25 Jun 1996, now patented, Pat. No. US 5698523, issued on 16 Dec 1997 which is a continuation of Ser. No. US 1995-420859, filed on 19 Apr 1995, now abandoned which is a continuation-in-part of Ser. No. US 1994-252798, filed on 2 Jun 1994, now abandoned
DT Utility
FS Granted
LN.CNT 1983
INCL INCLM: 514/019.000
INCLS: 548/537.000
NCL NCLM: 514/019.000
NCLS: 548/537.000

IC [6]
ICM: A61K038-05
ICS: C07D207-09
EXF 548/537; 514/19
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 4 OF 21 USPATFULL on STN
AN 1999:128716 USPATFULL
TI Peptide, peptide analog and amino acid analog protease inhibitors
IN Munoz, Benito, San Diego, CA, United States
McDonald, Ian A., San Diego, CA, United States
Albrecht, Elisabeth, San Diego, CA, United States
PA SIBIA Neurosciences, Inc., La Jolla, CA, United States (U.S. corporation)
PI US 5969100 19991019 <--
AI US 1995-403420 19950313 (8)
RLI Continuation-in-part of Ser. No. US 1995-369422, filed on 6 Jan 1995, now patented, Pat. No. US 5804560
DT Utility
FS Granted
LN.CNT 3687
INCL INCLM: 530/331.000
INCLS: 514/019.000; 514/018.000; 562/575.000
NCL NCLM: 530/331.000
NCLS: 562/575.000
IC [6]
ICM: A61K038-06
EXF 514/18; 514/19; 530/331; 562/575
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 5 OF 21 USPATFULL on STN
AN 1999:106562 USPATFULL
TI Acylated enol derivatives of .alpha.-ketoesters and .alpha.-ketoamides
IN Peet, Norton P., Cincinnati, OH, United States
Burkhart, Joseph P., Plainfield, IN, United States
Mehdi, Shujaath, West Chester, OH, United States
PA Hoechst Marion Roussel, Inc., Bridgewater, NJ, United States (U.S. corporation)
PI US 5948886 19990907 <--
AI US 1997-978096 19971125 (8)
RLI Continuation of Ser. No. US 1996-754081, filed on 20 Nov 1996, now abandoned
PRAI US 1996-31083P 19961201 (60)
DT Utility
FS Granted
LN.CNT 1641
INCL INCLM: 530/330.000
INCLS: 530/331.000; 514/018.000; 514/851.000
NCL NCLM: 530/330.000
NCLS: 514/018.000; 514/851.000; 530/331.000
IC [6]
ICM: C07K005-00
EXF 530/330; 530/331; 514/18; 514/851
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 6 OF 21 USPATFULL on STN
AN 1999:61253 USPATFULL
TI Peptide derivatives
IN Stein, Mark Morris, Wilmington, DE, United States
Trainor, Diane Amy, Glen Mills, PA, United States
PA Zeneca Inc., Wilmington, DE, United States (U.S. corporation)
PI US 5907068 19990525 <--

AI US 1992-941001 19920904 (7)
RLI Division of Ser. No. US 1990-491757, filed on 9 Mar 1990, now patented, Pat. No. US 5194588 which is a division of Ser. No. US 1987-5538, filed on 20 Jan 1987, now patented, Pat. No. US 4910190 which is a continuation-in-part of Ser. No. US 1986-821150, filed on 21 Jan 1986, now abandoned
PRAI GB 1985-1522 19850122
GB 1985-1523 19850122
GB 1985-1524 19850122
DT Utility
FS Granted
LN.CNT 5465
INCL INCLM: 568/713.000
NCL NCLM: 568/713.000
IC [6]
ICM: C07C079-18
EXF 530/331; 568/705; 568/712; 568/713
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 7 OF 21 USPATFULL on STN
AN 1999:22082 USPATFULL
TI Methods of treating neurodegenerative disorders using protease inhibitors
IN Munoz, Benito, San Diego, CA, United States
McDonald, Ian A., San Diego, CA, United States
Albrecht, Elisabeth, San Diego, CA, United States
PA Sibia Neurosciences, Inc., La Jolla, CA, United States (U.S. corporation)
PI US 5872101 19990216 <--
AI US 1995-444361 19950518 (8)
RLI Continuation of Ser. No. US 1995-403420, filed on 13 Mar 1995 which is a continuation-in-part of Ser. No. US 1995-369422, filed on 6 Jan 1995
DT Utility
FS Granted
LN.CNT 3945
INCL INCLM: 514/018.000
INCLS: 514/018.000; 530/331.000; 562/575.000; 562/562.000; 562/445.000; 562/567.000
NCL NCLM: 514/018.000
NCLS: 530/331.000; 562/445.000; 562/562.000; 562/567.000; 562/575.000
IC [6]
ICM: A61K038-05
EXF 514/18; 514/19; 530/331; 562/575; 562/562; 562/445; 562/567
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 8 OF 21 USPATFULL on STN
AN 1999:12911 USPATFULL
TI Methods of treating neurodegenerative disorders using protease inhibitors
IN Munoz, Benito, San Diego, CA, United States
McDonald, Ian A., San Diego, CA, United States
Albrecht, Elisabeth, San Diego, CA, United States
PA Sibia Neurosciences, Inc., La Jolla, CA, United States (U.S. corporation)
PI US 5863902 19990126 <--
AI US 1995-444912 19950518 (8)
RLI Continuation of Ser. No. US 1995-403420, filed on 13 Mar 1995 which is a continuation-in-part of Ser. No. US 1995-369422, filed on 6 Jan 1995
DT Utility
FS Granted
LN.CNT 3888
INCL INCLM: 514/019.000

INCLS: 530/331.000; 562/575.000; 562/545.000; 514/018.000
NCL NCLM: 514/019.000
NCLS: 514/018.000; 530/331.000; 562/545.000; 562/575.000
IC [6]
ICM: A61K038-05
EXF 514/18; 514/19; 530/331
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 9 OF 21 USPATFULL on STN
AN 1998:36728 USPATFULL
TI Peptidase inhibitors
IN Bey, Philippe, Cincinnati, OH, United States
Angelastro, Michael R., Cincinnati, OH, United States
Mehdi, Shujaath, Cincinnati, OH, United States
PA Merrell Pharmaceuticals Inc., Cincinnati, OH, United States (U.S. corporation)
PI US 5736520 19980407 <--
AI US 1995-434959 19950504 (8)
RLI Division of Ser. No. US 1994-214991, filed on 21 Mar 1994 which is a continuation of Ser. No. US 1992-861775, filed on 1 Apr 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-750439, filed on 20 Aug 1991, now abandoned which is a continuation of Ser. No. US 1989-454803, filed on 21 Dec 1989, now abandoned which is a continuation-in-part of Ser. No. US 1989-439201, filed on 20 Nov 1989, now abandoned which is a continuation-in-part of Ser. No. US 1989-416817, filed on 4 Oct 1989, now abandoned which is a continuation-in-part of Ser. No. US 1988-254762, filed on 7 Oct 1988, now abandoned
DT Utility
FS Granted
LN.CNT 1021
INCL INCLM: 514/019.000
INCLS: 526/595.000
NCL NCLM: 514/019.000
IC [6]
ICM: A61K038-05
EXF 514/18; 514/19; 526/575
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 10 OF 21 USPATFULL on STN
AN 1998:25212 USPATFULL
TI Peptide derivatives
IN Edwards, Philip Duke, Claymont, DE, United States
Schwartz, John Anthony, Wilmington, DE, United States
Stein, Mark Morris, Wilmington, DE, United States
Trainor, Diane Amy, Glen Mills, PA, United States
Wildonger, Richard Alan, Newark, DE, United States
PA Zeneca Inc., Wilmington, DE, United States (U.S. corporation)
PI US 5726158 19980310 <--
AI US 1995-467333 19950606 (8)
RLI Continuation of Ser. No. US 1990-482617, filed on 21 Feb 1990, now abandoned which is a division of Ser. No. US 1987-5538, filed on 20 Jan 1987, now patented, Pat. No. US 4910190 which is a continuation-in-part of Ser. No. US 1986-821150, filed on 21 Jan 1986, now abandoned
PRAI GB 1985-1522 19850122
GB 1985-1523 19850122
GB 1985-1524 19850122
DT Utility
FS Granted
LN.CNT 5961
INCL INCLM: 514/019.000
INCLS: 530/330.000; 530/331.000

NCL NCLM: 514/019.000
NCLS: 530/330.000; 530/331.000
IC [6]
ICM: A61K038-06
ICS: A61K038-07
EXF 514/19; 530/330; 530/331
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 11 OF 21 USPATFULL on STN
AN 97:118015 USPATFULL
TI Acylated enol derivatives as prodrugs of elastase inhibitors
IN Peet, Norton P., Cincinnati, OH, United States
Burkhart, Joseph P., West Chester, OH, United States
Mehdi, Shujaath, West Chester, OH, United States
PA Merrell Pharmaceuticals Inc., Cincinnati, OH, United States (U.S. corporation)
PI US 5698523 19971216 <--
AI US 1996-670136 19960625 (8)
RLI Continuation of Ser. No. US 1995-420859, filed on 19 Apr 1995, now abandoned which is a continuation-in-part of Ser. No. US 1994-252798, filed on 2 Jun 1994, now abandoned
DT Utility
FS Granted
LN.CNT 2060
INCL INCLM: 514/018.000
INCLS: 514/019.000; 514/237.200; 514/423.000; 548/537.000; 560/250.000; 560/253.000; 544/141.000; 530/330.000; 530/331.000
NCL NCLM: 514/018.000
NCLS: 514/019.000; 514/237.200; 514/423.000; 530/330.000; 530/331.000; 544/141.000; 548/537.000; 560/250.000; 560/253.000
IC [6]
ICM: C07D043-12
ICS: C07K005-083; A61K038-06
EXF 530/330; 530/331; 514/18; 514/19; 514/237.2; 514/423; 548/537; 560/250; 560/253; 544/141
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 12 OF 21 USPATFULL on STN
AN 95:41068 USPATFULL
TI 1-alkyl-2-hydroxy-2-trifluoromethyl ethylamines
IN Stein, Mark M., Wilmington, DE, United States
Trainor, Diane A., Glen Mills, PA, United States
PA Zeneca Inc., Wilmington, DE, United States (U.S. corporation)
PI US 5414132 19950509 <--
AI US 1992-940932 19920904 (7)
RLI Division of Ser. No. US 1990-491757, filed on 9 Mar 1990, now patented, Pat. No. US 5194588 which is a division of Ser. No. US 1987-5538, filed on 20 Jan 1987, now patented, Pat. No. US 4910190 which is a continuation-in-part of Ser. No. US 1986-821150, filed on 21 Jan 1986, now abandoned
PRAI GB 1985-1522 19850122
GB 1985-1523 19850122
GB 1985-1524 19850122
DT Utility
FS Granted
LN.CNT 5536
INCL INCLM: 564/503.000
NCL NCLM: 564/503.000
IC [6]
ICM: C07C215-08
EXF 564/503
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 13 OF 21 USPATFULL on STN
AN 93:63173 USPATFULL
TI Tetrahydroisoquinoline amides
IN Skiles, Jerry W., Brookfield, CT, United States
PA Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, United States (U.S. corporation)
PI US 5232928 19930803 <--
AI US 1991-792130 19911114 (7)
RLI Continuation of Ser. No. US 1990-536912, filed on 12 Jun 1990, now abandoned which is a continuation of Ser. No. US 1989-385140, filed on 25 Jul 1989, now abandoned
DT Utility
FS Granted
LN.CNT 769
INCL INCLM: 514/291.000
      INCLS: 514/307.000; 546/090.000; 546/146.000; 546/147.000
NCL NCLM: 514/291.000
      NCLS: 514/307.000; 546/090.000; 546/146.000; 546/147.000
IC [5]
      ICM: A61K031-47
      ICS: C07D217-16
EXF 546/146; 546/147; 546/90; 514/291; 514/307
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 14 OF 21 USPATFULL on STN
AN 93:50536 USPATFULL
TI N-substituted amides
IN Skiles, Jerry W., Brookfield, CT, United States
PA Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, United States (U.S. corporation)
PI US 5221665 19930622 <--
AI US 1991-686918 19910416 (7)
RLI Continuation of Ser. No. US 1989-426069, filed on 27 Oct 1989, now abandoned
DT Utility
FS Granted
LN.CNT 1435
INCL INCLM: 514/018.000
      INCLS: 514/017.000; 530/330.000
NCL NCLM: 514/018.000
      NCLS: 514/017.000; 530/330.000
IC [5]
      ICM: A61K037-02
      ICS: C07K005-10; C07K007-06
EXF 514/17; 514/18; 530/330
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 15 OF 21 USPATFULL on STN
AN 93:20683 USPATFULL
TI Aminoalcohol intermediates for peptide derivatives
IN Edwards, Philip D., Claymont, DE, United States
      Schwartz, John A., Wilmington, DE, United States
      Stein, Mark M., Wilmington, DE, United States
      Trainor, Diane A., Glen Mills, PA, United States
      Wildonger, Richard A., Newark, DE, United States
PA ICI Americas Inc., Wilmington, DE, United States (U.S. corporation)
PI US 5194588 19930316 <--
AI US 1990-491757 19900309 (7)
RLI Division of Ser. No. US 1987-5538, filed on 20 Jan 1987, now patented, Pat. No. US 4910190 which is a continuation-in-part of Ser. No. US 1986-821150, filed on 21 Jan 1986, now abandoned

PRAI GB 1985-1522 19850122
GB 1985-1523 19850122
GB 1985-1524 19850122
DT Utility
FS Granted
LN.CNT 5515
INCL INCLM: 530/331.000
INCLS: 546/225.000; 546/227.000; 548/536.000; 548/537.000; 548/538.000; 548/953.000
NCL NCLM: 530/331.000
NCLS: 546/225.000; 546/227.000; 548/536.000; 548/537.000; 548/538.000; 548/953.000
IC [5]
ICM: A61K037-02
ICS: C07K005-06; C07K005-08; C07K005-10
EXF 514/18; 514/19; 530/331; 530/330; 546/225; 546/227; 548/536; 548/537; 548/538; 548/953
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 16 OF 21 USPATFULL on STN
AN 92:95061 USPATFULL
TI Heterocyclic ketones
IN Edwards, Philip D., Claymont, DE, United States
Lewis, Joseph J., West Chester, PA, United States
Perkins, Charles W., Wilmington, DE, United States
Trainor, Diane A., Glen Mills, PA, United States
Wildonger, Richard A., Morgan Hollow, PA, United States
PA ICI Americas Inc., Wilmington, DE, United States (U.S. corporation)
PI US 5164371 19921117 <--
AI US 1988-193317 19880511 (7)
PRAI GB 1987-11050 19870511
GB 1988-3206 19880211
DT Utility
FS Granted
LN.CNT 2738
INCL INCLM: 514/018.000
INCLS: 514/019.000; 530/331.000; 544/297.000; 544/322.000; 544/333.000; 546/293.000; 546/306.000; 546/332.000; 548/159.000; 548/188.000; 548/217.000; 548/228.000; 548/233.000; 548/237.000
NCL NCLM: 514/018.000
NCLS: 514/019.000; 530/331.000; 544/297.000; 544/322.000; 544/333.000; 546/293.000; 546/306.000; 546/332.000; 548/110.000; 548/159.000; 548/179.000; 548/188.000; 548/205.000; 548/217.000; 548/228.000; 548/233.000; 548/235.000; 548/237.000
IC [5]
ICM: C07D237-08
ICS: C07D239-06; C07K005-08; A61K037-02
EXF 514/18; 514/19; 530/331; 548/178; 548/180; 548/182; 548/184; 548/192; 548/194; 548/204; 548/217; 548/228; 548/233; 548/236; 548/159; 548/188; 548/237; 544/297; 544/322; 544/333; 546/299; 546/332; 546/306
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 17 OF 21 USPATFULL on STN
AN 91:82198 USPATFULL
TI Peptide derivatives
IN Edwards, Philip D., Claymont, DE, United States
Schwartz, John A., Wilmington, all, DE, United States
Stein, Mark M., Wilmington, all, DE, United States
Trainor, Diane A., Glen Mills, PA, United States
Wildonger, Richard A., Elmwood, DE, United States
PA ICI Americas Inc., Wilmington, DE, United States (U.S. corporation)
PI US 5055450 19911008 <--

AI US 1990-493025 19900313 (7)
RLI Division of Ser. No. US 1987-5538, filed on 20 Jan 1987, now patented, Pat. No. US 4910190 which is a continuation-in-part of Ser. No. US 1986-821150, filed on 21 Jan 1986, now abandoned
PRAI GB 1985-1522 19850122
GB 1985-1523 19850122
GB 1985-5124 19850122
DT Utility
FS Granted
LN.CNT 6077
INCL INCLM: 514/019.000
INCLS: 548/953.000; 548/537.000; 548/538.000; 548/253.000; 530/330.000; 530/331.000; 546/225.000; 546/226.000; 546/245.000; 546/227.000
NCL NCLM: 514/019.000
NCLS: 530/330.000; 530/331.000; 546/225.000; 546/226.000; 546/227.000; 546/245.000; 548/253.000; 548/537.000; 548/538.000; 548/953.000
IC [5]
ICM: A61K037-64
EXF 548/953; 548/537; 548/538; 548/253; 548/536; 546/226; 546/225; 546/245; 546/227; 530/330; 530/331; 514/19
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 18 OF 21 USPATFULL on STN
AN 90:36303 USPATFULL
TI Difluoro keto compounds and their use as HLE inhibitors
IN Trainor, Diane A., Glen Mills, PA, United States
Stein, Mark M., Wilmington, DE, United States
PA ICI Americas Inc., Wilmington, DE, United States (U.S. corporation)
PI US 4923890 19900508 <--
AI US 1987-51951 19870519 (7)
RLI Continuation-in-part of Ser. No. US 1987-3993, filed on 16 Jan 1987, now abandoned
PRAI GB 1986-13704 19860605
DT Utility
FS Granted
LN.CNT 2394
INCL INCLM: 424/046.000
INCLS: 514/005.000; 514/011.000; 514/381.000; 514/423.000; 548/253.000; 548/536.000; 548/537.000; 548/538.000
NCL NCLM: 424/046.000
NCLS: 514/005.000; 514/011.000; 514/381.000; 514/423.000; 548/253.000; 548/536.000; 548/537.000; 548/538.000
IC [5]
ICM: A61K009-12
ICS: A61K031-40; A61K009-14; C07D207-09
EXF 548/253; 548/537; 548/536; 548/538; 514/381; 514/423; 514/5; 514/11; 424/46
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 19 OF 21 USPATFULL on STN
AN 90:21543 USPATFULL
TI Peptide derivatives
IN Bergeson, Scott H., Wilmington, DE, United States
Edwards, Philip D., Claymont, DE, United States
Schwartz, John A., Wilmington, DE, United States
Shaw, Andrew, Kennett Square, PA, United States
Stein, Mark M., Wilmington, DE, United States
Trainor, Diane A., Glen Mills, PA, United States
Wildonger, Richard A., Newark, DE, United States
Wolanin, Donald J., Wilmington, DE, United States
PA ICI Americas Inc., Wilmington, DE, United States (U.S. corporation)
PI US 4910190 19900320 <--

AI US 1987-5538 19870120 (7)
RLI Continuation-in-part of Ser. No. US 1986-821150, filed on 21 Jan 1986, now abandoned
PRAI GB 1985-1522 19850122
GB 1985-1523 19850122
GB 1985-1524 19850122
DT Utility
FS Granted
LN.CNT 5524
INCL INCLM: 514/019.000
INCLS: 548/953.000; 548/536.000; 548/537.000; 548/538.000; 546/225.000; 546/227.000
NCL NCLM: 514/019.000
NCLS: 546/225.000; 546/227.000; 548/536.000; 548/537.000; 548/538.000; 548/953.000
IC [4]
ICM: A61K037-64
EXF 530/330; 530/331; 514/19; 548/953; 548/536; 548/537; 548/538; 546/225; 546/227
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 20 OF 21 USPATFULL on STN
AN 89:92486 USPATFULL
TI Selected difluoro derivatives
IN Trainor, Diane A., Glen Mills, PA, United States
Stein, Mark M., Wilmington, DE, United States
PA ICI Americas Inc., Wilmington, DE, United States (U.S. corporation)
PI US 4880780 19891114 <--
AI US 1987-58079 19870604 (7)
RLI Continuation-in-part of Ser. No. US 1986-872106, filed on 6 Jun 1986, now abandoned
PRAI GB 1985-14436 19850607
GB 1985-14438 19850607
GB 1985-14440 19850607
DT Utility
FS Granted
LN.CNT 2503
INCL INCLM: 514/018.000
INCLS: 530/331.000
NCL NCLM: 514/018.000
NCLS: 530/331.000
IC [4]
ICM: A61K037-43
ICS: C07K005-08
EXF 514/18; 530/331
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 21 OF 21 USPATFULL on STN
AN 89:84234 USPATFULL
TI Difluoro peptide compounds
IN Trainor, Diane A., Glen Mills, PA, United States
PA ICI Americas Inc., Wilmington, DE, United States (U.S. corporation)
PI US 4873221 19891010 <--
AI US 1987-51952 19870519 (7)
PRAI GB 1986-13703 19860605
DT Utility
FS Granted
LN.CNT 1691
INCL INCLM: 514/018.000
INCLS: 514/019.000; 530/331.000
NCL NCLM: 514/018.000
NCLS: 514/019.000; 530/331.000

IC [4]
ICM: A61K037-43
ICS: C07K005-08
EXF 530/331; 514/18; 514/19
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d 12 1-21 ab, kwic

L2 ANSWER 1 OF 21 USPATFULL on STN
AB Methods of use of compounds and compounds for the treatment of disorders characterized by the cerebral deposition of amyloid are provided. Among the compounds are those of formulae (I), (II) and (III): ##STR1## in which R.sub.1 is preferably 2-methyl propene, 2-butene, norleucine; R.sub.2, R.sub.4, and R.sub.8 are each independently methyl or ethyl; R.sub.3 is preferably iso-butyl or phenyl; R.sub.5 is preferably iso-butyl; R.sub.6 is H or methyl; R.sub.7 --(Q).sub.n is preferably benzyloxycarbonyl or acetyl; Q is preferably --C(O)--; R.sub.B is preferbly iso-butyl; R.sub.A =--(T).sub.m --(D).sub.m --R.sub.1, is which T is preferably oxygen or carbon, and D is preferably a mono-unsaturated C.sub.3-4 alkenyl being more preferred; and X is an alcohol, particularly a secondary alcohol.
PI US 6017887 20000125 <--
SUMM . . . serine protease. This enzyme has been implicated as a pathogenic agent in a variety of disorders, including pulmonary emphysema, rheumatoid **arthritis**, adult respiratory distress syndrome (ARDS), glomerulonephritis and cystic fibrosis [see, e.g., Skiles et al. (1992) J. Med. Chem. 35:641-662; Angelastro. . .
SUMM . . . alkyl type protecting groups such as triphenylmethyl (trityl) and benzyl (Bn); and (7) trialkylsilane protecting groups such as trimethylsilane, 4-[-(4-chlorophenyl) **sulfonylaminocarbonyl**] phenyl carbonyl, and 4-[-(4-bromophenyl) **sulfonylaminocarbonyl**] phenyl carbonyl. The preferred .alpha.-amino protecting group is t-butyloxycarbonyl (BOC); its use as an .alpha.-amino protecting group for amino acids. . .

L2 ANSWER 2 OF 21 USPATFULL on STN
AB This invention relates to compounds which are inhibitors of elastase, particularly human neutrophil elastase, and to novel processes for making the same. As inhibitors of human neutrophil elastase, the compounds are useful in the treatment of a patient afflicted with a neutrophil associated inflammatory disease.
PI US 6008196 19991228 <--
WO 9533762 19951214 <--
SUMM . . . contributing to the tissue destruction associated with a number of inflammatory diseases such as chronic bronchitis, cystic fibrosis, and rheumatoid **arthritis**. J. L. Malech and J. I. Gallin, New Engl. J. Med., 317(11), 687 (1987). Elastase possesses a broad range of. . .
SUMM . . . as inhibitors of elastase. The compounds of formula I exhibit an anti-inflammatory effect useful in the treatment of gout, rheumatoid **arthritis** and other inflammatory diseases, such as adult respiratory distress syndrome, septicemia, disseminated intravascular coagulation, cystic fibrosis, chronic bronchitis, chronic obstructive. . .
SUMM . . . to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolyl, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . .
DETD . . . distress syndrome, septicemia, chronic bronchitis, inflammatory bowel disease (particularly ulcerative colitis or Crohn's disease),

disseminated intravascular coagulation, gout and rheumatoid **arthritis**. Compounds of formulae (I)-(IV) which are particularly preferred for the treatment of neutrophil associated inflammatory diseases include:

DETD . . . to emphysema, cystic fibrosis, adult respiratory distress syndrome, chronic bronchitis, inflammatory bowel disease, septicemia, disseminated intravascular coagulation, gout and rheumatoid **arthritis**. However, it is understood that the present invention is not limited by any particular theory or proposed mechanism to explain. . .

L2 ANSWER 3 OF 21 USPATFULL on STN

AB This invention relates to acylated enol derivatives of known elastase inhibitors. These compounds are useful in the treatment of various inflammatory diseases, including cystic fibrosis and emphysema or as prodrugs of compounds which are useful in the treatment of said diseases.

PI US 5972897 19991026 <--

SUMM . . . contributing to the tissue destruction associated with a number of inflammatory diseases such as chronic bronchitis, cystic fibrosis, and rheumatoid **arthritis**. J. L. Malech and J. I. Gallin, New Engl. J. Med., 317(11), 687 (1987). Elastase possesses a broad range of. . .

SUMM . . . anti-inflammatory effect useful in the treatment of emphysema, cystic fibrosis, adult respiratory distress syndrome, septicemia, disseminated intravascular coagulation, gout, rheumatoid **arthritis**, chronic bronchitis and inflammatory bowel disease; or are prodrugs of compounds which exhibit such effects.

DETD (E)-N-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[2-(acetyloxy)-3,3,3-trifluoro-1-(1-methylethyl)-1-propenyl]-L-prolinamide.

DETD . . . to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolyl, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . .

DETD Preparation of (E)-N-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[2-(acetyloxy)-3,3,3-trifluoro-1-(1-methylethyl)-1-propenyl]-L-prolinamide ##STR46## Method A; step a: N-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[3,3,3-trifluoro-1-(1-methylethyl)-2-oxopropyl]-L-prolinamide (54)

DETD To a stirred light suspension of 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoic acid (0.68 g, 2.02 mmol; EP Pat. Appl. Publ. No. 0189305 B1) in CH.sub.2 Cl.sub.2 (18 mL) and DMF (2. . .

DETD (E)-N-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[2-(acetyloxy)-3,3,3-trifluoro-1-(1-methylethyl)-1-propenyl]-L-prolinamide (MDL 105,928)

DETD . . . formula I will be particularly useful nalude: emphysema, cystic fibrosis, adult respiratory distress syndrome, septicemia, disseminated intravascular coagulation, gout, rheumatoid **arthritis**, chronic bronchitis and inflammatory bowel disease. Compounds of formula I which are particularly preferred for the treatment of neutrophil associated. . .

DETD (E)-N-[4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[2-(acetyloxy)-3,3,3-trifluoro-1-(1-methylethyl)-1-propenyl]-L-prolinamide.

DETD . . . elastase-mediated diseases including but not limited to emphysema, cystic fibrosis, adult rspiratory distress syndrome, septicemia, disseminated intravascular coagulation, gout, rheumatoid **arthritis**, chronic bronchitis and inflammatory bowel disease. However, it is understood that the present invention is not limited by

any particular. . .

CLM What is claimed:
9. A compound of claim 1 wherein said compound is (E)-N-[4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[2-(acetyloxy)-3,3,3-trifluoro-1-(1-methylethyl)-1-propenyl]-L-prolinamide.

L2 ANSWER 4 OF 21 USPATFULL on STN

AB Methods of use of compounds and compounds for the treatment of disorders characterized by the cerebral deposition of amyloid are provided. Among the compounds are those of formulae (I), (II) and (III): ##STR1## in which R.sub.1 is preferably 2-methyl propene, 2-butene, norleucine; R.sub.2, R.sub.4, and R.sub.8 are each independently methyl or ethyl; R.sub.3 is preferably iso-butyl or phenyl; R.sub.5 is preferably iso-butyl; R.sub.6 is H or methyl; R.sub.7 --(Q).sub.n is preferably benzyloxycarbonyl or acetyl; Q is preferably --C(O)--; R.sub.B is preferbly iso-butyl; R.sub.A =--(T).sub.m --(D).sub.m --R.sub.1, is which T is preferably oxygen or carbon, and D is preferably a mono-unsaturated C.sub.3-4 alkenyl being more preferred; and X is an alcohol, particularly a secondary alcohol.

PI US 5969100 19991019 <--

SUMM . . . serine protease. This enzyme has been implicated as a pathogenic agent in a variety of disorders, including pulmonary emphysema, rheumatoid **arthritis**, adult respiratory distress syndrome (ARDS), glomerulonephritis and cystic fibrosis [see, e.g., Skiles et al. (1992) J. Med. Chem. 35:641-662; Angelastro. . .

SUMM . . . (6) alkyl type protecting groups such as triphenylmethyl (trityl) and benzyl (Bn); and (7) trialkylsilane protecting groups such as trimethylsilane, 4-[-(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl carbonyl, and 4-[-(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl carbonyl. The preferred .alpha.-amino protecting group is t-butyloxycarbonyl (BOC); its use as an .alpha.-amino protecting group for amino acids is. . .

L2 ANSWER 5 OF 21 USPATFULL on STN

AB This invention relates to acylated enol derivatives of .alpha.-ketoesters and .alpha.-ketoamides. The compounds of this invention are either prodrugs of known elastase inhibitors or are elastase inhibitors in their own right and are useful in the treatment of various inflammatory diseases, including cystic fibrosis and emphysema.

PI US 5948886 19990907 <--

SUMM . . . contributing to the tissue destruction associated with a number of inflammatory diseases such as chronic bronchitis, cystic fibrosis, and rheumatoid **arthritis**. J. L. Malech and J. I. Gallin, New Engl. J. Med., 317(11), 687 (1987). Elastase possesses a broad range of. . .

SUMM K is hydrogen, acetyl, succinyl, benzoyl, t-butyloxycarbonyl, carbobenzyloxy, dansyl, isovaleryl, methoxysuccinyl, 1-adamantanesulphonyl, 1-adamantaneacetyl, 2-carboxybenzoyl, --C(O)N(CH.sub.3).sub.2, 4-((chlorophenyl)**sulfonylaminocarbonyl**)phenylcarbonyl, 4-((4-bromophenyl)**sulfonylaminocarbonyl**)phenylcarbonyl, 4-(**sulfonylaminocarbonyl**)phenylcarbonyl or is a group of the formulae ##STR2## wherein Z is N or CH, B is a group of the. . .

SUMM . . . anti-inflammatory effect useful in the treatment of emphysema, cystic fibrosis, adult respiratory distress syndrome, septicemia, disseminated intravascular coagulation, gout, rheumatoid **arthritis**, chronic bronchitis and inflammatory bowel disease; or are prodrugs of compounds which exhibit such effects.

SUMM . . . In addition, amino protecting group K wherein K is acetyl, succinyl, benzoyl, t-butyloxycarbonyl, carbobenzyloxy, dansyl,

isovaleryl, methoxysuccinyl, 1-adamantanesulphonyl, 1-adamantaneacetyl, 2-carboxybenzoyl, 4-((chlorophenyl)**sulfonylaminocarbonyl**)-phenylcarbonyl, 4-((4-bromophenyl)**sulfonylaminocarbonyl**)-phenylcarbonyl, and 4-(**sulfonylaminocarbonyl**)phenylcarbonyl are described in European Patent Appl. Publ. No. 363 284, published Apr. 11, 1990 and U.S. Pat. No. 4,910,190, issued. . .

DETD Preparation of L-Prolinamide, N-[4-[[[(4-chlorohenyl)sulfonyl]amino]carbonyl]benzoyl]-L-valyl-N-[2-(acetyloxy)-3-amino-1-(1-methylethyl)-3-oxo-1-propenyl]-, (E) ##STR25## a) Preparation of N-(4-((4-chlorophenyl)-**sulfonylaminocarbonyl**)phenylcarbonyl-Val-Pro-Val-COOH

DETD Scheme G, step a; Dissolve N-(4-((4-chlorophenyl)-**sulfonylaminocarbonyl**)phenylcarbonyl-Val-Pro-Val-CO.sub.2 CH.sub.3 (677 mg, 1.0 mmol) in a THF:methanol:water (1:1:1) solvent mixture (30 mL) and treat with 1.0 N aqueous lithium. . .

DETD b) Preparation of N-(4-((4-chlorophenyl)-**sulfonylaminocarbonyl**)phenylcarbonyl-Val-Pro-Val-CONH.sub.2

DETD Preparation of L-Prolinamide, N-[4-[[[(4-chlorophenyl)sulfonyl]amino]carbonyl]benzoyl]-L-valyl-N-[1-(1-methylethyl)-3-oxo-2-(acetyloxy)-3-(phenylamino)-1-propenyl]-, (E) ##STR26## a) Preparation of N-(4-((4-chlorophenyl)-**sulfonylaminocarbonyl**)phenylcarbonyl-Val-Pro-Val-CONHC.sub.6 H.sub.5

DETD . . . formula I will be particularly useful include: emphysema, cystic fibrosis, adult respiratory distress syndrome, septicemia, disseminated intravascular coagulation, gout, rheumatoid **arthritis**, chronic bronchitis and inflammatory bowel disease. Compounds of formula I which are particularly preferred for the treatment of neutrophil associated. . .

DETD . . . elastase-mediated diseases including but not limited to emphysema, cystic fibrosis, adult rspiratory distress syndrome, septicemia, disseminated intravascular coagulation, gout, rheumatoid **arthritis**, chronic bronchitis and inflammatory bowel disease. However, it is understood that the present invention is not limited by any particular. . .

CLM What is claimed is:

. . . bVal, Pro or is deleted; K is hydrogen, acetyl, succinyl, benzoyl, t-butyloxycarbonyl, carbobenzyloxy, dansyl, isovaleryl, methoxysuccinyl, 1-adamantanesulphonyl, 1-adamantaneacetyl, 2-carboxybenzoyl, --C(O)N(CH.sub.3).sub.2, 4-((chlorophenyl)**sulfonylaminocarbonyl**)phenyl-carbonyl, 4-((4-bromophenyl)**sulfonylaminocarbonyl**)phenyl-carbonyl, 4-(**sulfonylaminocarbonyl**)phenylcarbonyl or is a group of the formulae ##STR43## wherein Z is N or CH, B is a group of the. . .

. . . Ile, Val, or Ala; P.sub.4 is Ala, Pro or is deleted; and K is acetyl, succinyl, t-butyloxycarbonyl, carbobenzyloxy, methoxysuccinyl, --C(O)N(CH.sub.3).sub.2, 4-((chlorophenyl)**sulfonylaminocarbonyl**)phenyl-carbonyl, 4-((4-bromophenyl)**sulfonylaminocarbonyl**)phenyl-carbonyl, 4-(**sulfonylaminocarbonyl**)phenylcarbonyl or is a group of the formula ##STR45## wherein Z is N or CH, B is a group of the. . .

. . . 3. A compound of claim 2 wherein R.sub.1 is isopropyl; P.sub.2 is Pro; and K is acetyl, t-butyloxycarbonyl, succinyl, methyoxysuccinyl, 4-((chlorophenyl)**sulfonylaminocarbonyl**)-phenylcarbonyl, or is a group of the formula ##STR47## wherein Z is N or CH, B is a group of the. . .

L2 ANSWER 6 OF 21 USPATFULL on STN

AB The invention concerns pharmaceutically useful trifluoromethyl ketone substituted di-, tri- and tetra-peptide derivatives of the formulae Ia, Ib, Ic set out hereinafter, and salts thereof which are inhibitors of human leukocyte elastase. Also described herein are pharmaceutical compositions containing a peptide derivative and processes and intermediates for use in the manufacture of the peptide derivatives.

PI US 5907068 19990525 <--

SUMM . . . in pharmacological, diagnostic and related studies and in the treatment of tissue degenerative diseases such as pulmonary emphysema, atherosclerosis, rheumatoid **arthritis** and osteo **arthritis** in warm blooded animals. The invention also includes intermediates useful in the synthesis of these peptide derivatives, processes for preparing. . .

SUMM (x) acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsufonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . by a member selected from carboxy, alkoxycarbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . .

SUMM . . . a member selected from carboxy, alkoxycarbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . .

SUMM (x) acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons), and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing from 1 to 15 carbons, and provided that when the acylsulfonamido contains an aryl the aryl may be further. . .

SUMM . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons (e.g., 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl or 4-[(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl);

SUMM (x) ethyl substituted by an acylsulfonamido selected from the group consisting of 2-(methylsulfonylaminocarbonyl)ethyl, 2-(phenylsulfonylaminocarbonyl)ethyl, 2-[(1-adamantyl) **sulfonylaminocarbonyl**]ethyl, and 2-[(1-naphthyl) **sulfonylaminocarbonyl**]ethyl;

SUMM . . . carboxy, methoxy, ethoxy, methoxycarbonyl, ethoxycarbonyl, methylcarbonylamino, an acylsulfonamido containing 2 carbons, (e.g., 4-(methylsulfonaminocarbonyl)phenyl), an acylsulfonamido containing 7 carbons (e.g., 4-(phenylsulfonylaminocarbonyl)phenyl, 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**)phenyl, or [(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl), an acylsulfonamido containing 11 carbons (e.g., 4(1-naphthylsulfonylaminocarbonylphenyl), an acylsulfonamido containing 14 carbons (e.g., 4-(4-bromophenylsulfonylamino(benzyl)carbonyl)phenyl); and an aryl group containing 6. . .

SUMM . . . ethenyl group substituted by a member selected from the group consisting of carboxy, ethoxycarbonyl, ureidocarbonyl (e.g., Z-2-(aminocarbonyl amino)ethenyl)), acylsulfonamidophenyl (e.g., 2-[4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl]ethenyl), and 4-carboxyphenyl (e.g., E-2-(4-carboxyphenyl)ethenyl;

SUMM . . . a warm-blooded animal in need thereof , particularly a human, for the treatment of conditions of pulmonary emphysema, atherosclerosis, rheumatoid **arthritis**, and osteo **arthritis**, in particular for emphysema. The mode of administration may be oral, parenteral, including the subcutaneous deposit by means of an. . .

DETD 3(RS)-4-I(4-Nitrophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-NO.sub.2 .phi.)S(O.sub.2)NHCO].phi., R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-[4-f(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Br.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD b. 3(RS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Br-.phi.)S(O.sub.2) NHC(O)].phi., R.sup.4 =H, A=CO, n=1).

DETD 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.4 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi.--, R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-[3-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]-phenyl]-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi.-(CH.sub.2).sub.2, R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-E-[3-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]-phenyl3-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =E-[4-[(4-Cl.phi.)S--(O.sub.2)NHC(O)].phi.--CH.dbd.CH--, R.sup.4 =H, A=CO, n=1)

DETD 3R(or S)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxo-pentyl))-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[4-(Br.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD 3S(or R)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-

prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Br.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=OC, n=1)

DETD 3S(or R)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD 3R(or S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]-phenyl]carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =CH(CH.sub.3)CH.sub.3, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHCO].phi., R.sup.4 =H, A=CO, n=1)

DETD a. 1,1-Dimethylethyl 4-(4-chlorophenyl)**sulfonylaminocarbonyl** benzoate.

DETD b. 4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzenecarboxylic acid.

DETD c. 2(RS),3(SR)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =CH(CH.sub.3)CH.sub.3, R.sup.3 =4-[(4Cl-.phi.)S(O.sub.2)NHCO].phi., R.sup.4 =H, A=CO, n=1).

DETD d. 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =CH(CH.sub.3)CH.sub.3, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)--NHCO].phi., R.sup.4 =H, A=CO, n=1).

L2 ANSWER 7 OF 21 USPATFULL on STN

AB Methods of use of compounds and compounds for the treatment of disorders characterized by the cerebral deposition of amyloid are provided. Among the compounds are those of formulae (I), (II) and (III): ##STR1## in which R.sub.1 is preferably 2-methyl propene, 2-butene, norleucine; R.sub.2, R.sub.4, and R.sub.8 are each independently methyl or ethyl; R.sub.3 is preferably iso-butyl or phenyl; R.sub.5 is preferably iso-butyl; R.sub.6 is H or methyl; R.sub.7 --(Q).sub.n is preferably benzyloxycarbonyl or acetyl; Q is preferably --C(O)--; R.sub.8 is preferbly iso-butyl; R.sub.A =--(T).sub.m --(D).sub.m --R.sub.1, is which T is preferably oxygen or carbon, and D is preferably a mono-unsaturated C.sub.3-4 alkenyl being more preferred; and X is an alcohol, particularly a secondary alcohol.

PI US 5872101 19990216 <--

SUMM . . . serine protease. This enzyme has been implicated as a pathogenic agent in a variety of disorders, including pulmonary emphysema, rheumatoid **arthritis**, adult respiratory distress syndrome (ARDS), glomerulonephritis and cystic fibrosis [see, e.g., Skiles et al. (1992) J. Med. Chem. 35:641-662; Angelastro. . .

SUMM . . . (6) alkyl type protecting groups such as triphenylmethyl (trityl) and benzyl (Bn); (7) trialkylsilane protecting groups such as trimethylsilane, 4-[-(4-chlorophenyl) **sulfonylaminocarbonyl**] phenyl carbonyl, and 4-[-(4-bromophenyl) **sulfonylaminocarbonyl**] phenyl carbonyl. The preferred .alpha.-amino protecting group is t-butyloxycarbonyl (BOC); its use as an .alpha.-amino protecting group for amino acids. . .

L2 ANSWER 8 OF 21 USPATFULL on STN

AB Methods of use of compounds and compounds for the treatment of disorders

characterized by the cerebral deposition of amyloid are provided. Among the compounds are those of formulae (I), (II) and (III): ##STR1## in which R.sub.1 is preferably 2-methyl propene, 2-butene, norleucine; R.sub.2, R.sub.4, and R.sub.8 are each independently methyl or ethyl; R.sub.3 is preferably iso-butyl or phenyl; R.sub.5 is preferably iso-butyl; R.sub.6 is H or methyl; R.sub.7 -(Q).sub.n is preferably benzyloxycarbonyl or acetyl; Q is preferably --C(O)--; RB is preferbly iso-butyl; R.sub.A =--(T).sub.m --(D).sub.m --R.sub.1, is which T is preferably oxygen or carbon, and D is preferably a mono-unsaturated C.sub.3-4 alkenyl being more preferred; and X is an alcohol, particularly a secondary alcohol.

PI US 5863902 19990126 <--

SUMM . . . serine protease. This enzyme has been implicated as a pathogenic agent in a variety of disorders, including pulmonary emphysema, rheumatoid **arthritis**, adult respiratory distress syndrome (ARDS), glomerulonephritis and cystic fibrosis [see, e., Skiles et al. (1992) J. Med. Chem. 35:641-662; Angelastro. . .

SUMM . . . alkyl type protecting groups such as triphenylmethyl (trityl) and benzyl (Bn); and (7) trialkylsilane protecting groups such as trimethylsilane, 4-[-(4-chlorophenyl) **sulfonylaminocarbonyl**] phenyl carbonyl, and 4-[-(4-bromophenyl) **sulfonylaminocarbonyl**] phenyl carbonyl. The preferred .alpha.-amino protecting group is t-butyloxycarbonyl (BOC); its use as an .alpha.-amino protecting group for amino acids. . .

L2 ANSWER 9 OF 21 USPATFULL on STN

AB This invention relates to analogs of peptidase substrates in which the nitrogen atom of the scissile amide group of the substrate peptide has been replaced by H, an aldehyde, a substituted carbonyl or a substituted malonyl moiety. These analogs of the peptidase substrates provide specific enzyme inhibitors for a variety of proteases, the inhibition of which will have useful physiological consequences in a variety of disease states.

PI US 5736520 19980407 <--

SUMM . . . particularly those wherein the acylsulfonamido contains an aryl moiety (preferably phenyl) substituted by a halogen. The preferred --A--Rz moieties being 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl, 4-[(4-bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl and 4-[phenylsulfonylaminocarbonyl]phenylcarbonyl (said moieties being abbreviated as Cl.O slashed.-SAC-Bz, Br.O slashed.-SAC-Bz and .O slashed.-SAC-Bz, respectively)

SUMM The end-use application of the compounds (Ib) inhibiting Cathepsin G is the same as for human leucocyte inhibitors, including **arthritis** , gout and emphysema, but also embracing the treatment of glomerulonephritis and lung infestations caused by infections in the lung. For. . .

SUMM . . . secondary effects on platelet activation such as (for enhancing clot formation) leukocyte degranulation (for treating inflammation and immunological diseases, e.g. **arthritis**, emphysema, multiple sclerosis, and systemic lupus); (c) have a general inhibition of intracellular proteolysis, particularly for muscle cells, causing secondary. . .

L2 ANSWER 10 OF 21 USPATFULL on STN

AB The invention concerns pharmaceutically useful trifluoromethyl ketone substituted di-, tri- and tetra-peptide derivatives of the formulae Ia, Ib, Ic set out hereinafter, and salts thereof, which are inhibitors of human leukocyte elastase. Also described herein are pharmaceutical compositions containing a peptide derivative and processes and intermediates for use in the manufacture of the peptide derivatives.

PI US 5726158 19980310 <--

SUMM . . . in pharmacological, diagnostic and related studies and in the

treatment of tissue degenerative diseases such as pulmonary emphysema, atherosclerosis, rheumatoid **arthritis** and osteo **arthritis** in warm blooded animals. The invention also includes intermediates useful in the synthesis of these peptide derivatives, processes for preparing. . .

SUMM (x) acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsufonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . by a member selected from carboxy, alkoxycarbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . .

SUMM . . . a member selected from carboxy, alkoxycarbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . .

SUMM (x) acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons), and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing from 1 to 15 carbons, and provided that when the acylsulfonamido contains an aryl the aryl may be further. . .

SUMM . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons (e.g., 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl or 4-[(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl);

SUMM (x) ethyl substituted by an acylsulfonamido selected from the group consisting of 2-(methylsulfonylaminocarbonyl)ethyl, 2-

(phenylsulfonylaminocarbonyl)ethyl, 2-[(1-adamantyl)**sulfonylaminocarbonyl**]ethyl, and 2-[(1-naphthyl)**sulfonylaminocarbonyl**]ethyl;

SUMM . . . carboxy, methoxy, ethoxy, methoxycarbonyl, ethoxycarbonyl, methylcarbonylamino, an acylsulfonamido containing 2 carbons, (e.g., 4-(methylsulfonaminocarbonyl)phenyl), an acylsulfonamido containing 7 carbons (e.g., 4-(phenylsulfonylaminocarbonyl)phenyl, 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl, or [(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl), an acylsulfonamido containing 11 carbons (e.g., 4(1-naphthylsulfonylaminocarbonylphenyl), an acylsulfonamido containing 14 carbons (e.g., 4-(4-bromophenylsulfonylamino(benzyl)carbonyl)phenyl); and an aryl group containing 6. . .

SUMM (X) an ethenyl group substituted by a member selected from the group consisting of carboxy, ethoxycarbonyl, ureidocarbonyl (e.g., Z-2-(aminocarbonylamino)ethenyl)), acylsulfonamidophenyl (e.g.,2-[4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl]ethenyl), and 4-carboxyphenyl (e.g., E-2-(4-carboxyphenyl)ethenyl;

SUMM . . . to a warm-blooded animal in need thereof, particularly a human, for the treatment of conditions of pulmonary emphysema, atherosclerosis, rheumatoid **arthritis**, and osteo **arthritis**, in particular for emphysema. The mode of administration may be oral, parenteral, including the subcutaneous deposit by means of an. . .

DETD 3(RS)-4-[(4-Nitrophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxo-pentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-NO.sub.2 .O slashed.)S(O.sub.2)NHCO].O slashed., R.sup.4 =H, A=CO, n=1)

DETD 3 (RS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Br.O slashed.)S(O.sub.2)NHC(O)].O slashed., R.sup.4 =H, A=CO, n=1)

DETD b. 3(RS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Br-.O slashed.)S(O.sub.2) NHC(O)].O slashed., R.sup.4 =H, A=CO, n=1).

DETD 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH, R.sup.3 =4-[(4-Cl.O slashed.)S(O.sub.2)NHC(O)].O slashed.--, R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-[3-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl]-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Cl.O slashed.)S(O.sub.2)NHC(O)].O slashed.--(Ch.sub.2).sub.2, R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-E-[3-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl]-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =E-[4-[(4-Cl.O slashed.)S--(O.sub.2)NHC(O)].O slashed.--CH.dbd.CH--, R.sup.4 =H, A=CO, n=1)

DETD 3R(orS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxo-pentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[4-(Br.O slashed.)S(O.sub.2)NHC(O)].O slashed., R.sup.4 =H, A=CO, n=1)

DETD 3S(or R)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**

]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Br.O slashed.)S(O.sub.2)NHC(O)].O slashed., R.sup.4 =H, A=CO, n=1)

DETD 3S(or R)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Cl.O slashed.)S(O.sub.2)NHC(O)].O slashed., R.sup.4 =H, A=CO, n=1)

DETD 3R(or S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]-phenyl]carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Cl.O slashed.)S(O.sub.2)NHC(O)].O slashed., R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =CH(CH.sub.3)CH.sub.3, R.sup.3 =4-[(4-Cl.O slashed.)S(O.sub.2)NHCO].O slashed., R.sup.4 =H, A=CO, n=1)

DETD a. 1,1-Dimethylethyl 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoate.

DETD b. 4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzenecarboxylic acid.

DETD c. 2(RS),3(SR)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =CH(CH.sub.3)CH.sub.3, R.sup.3 =4-[(4Cl-.O slashed.)S(O.sub.2)NHCO].O slashed., R.sup.4 =H, A=CO, n=1).

DETD d. 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =CH(CH.sub.3)CH.sub.3, R.sup.3 =4-[(4-Cl.O slashed.)S(O.sub.2)--NHCO].O slashed., R.sup.4 =H, A=CO, n=1).

CLM What is claimed is:

. . . the aryl portion contains 6 carbons; (x) ethyl substituted by an acylsulfonamido selected from the group consisting of 2-(methylsulfonylaminocarbonyl)ethyl, 2-(phenylsulfonylaminocarbonyl)ethyl, 2-[(1-adamantyl)**sulfonylaminocarbonyl**]ethyl, and 2-[(1-naphthyl)**sulfonylaminocarbonyl**]ethyl; (y) an alkyl group containing 2 or 10 carbons and substituted by methoxycarbonyl; (z) an alkyl group containing 2 to. . .

. . . 33) 3(RS)-N.sup.2 -(4-Hydroxycarbonylphenyl)aminocarbonyl-N.sup.6 -phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 34) 3(RS)-(4-Hydroxycarbonylphenyl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 35) 3(RS)-(Tricyclo[3.3.1.1.sup.3,7]dec-1-yl)sulfonyl-L-.alpha.-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 36) 3(RS)-(4-Methoxycarbonylphenyl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 37) 3(RS)-(4-Hydroxycarbonylphenyl)aminocarbonyl-L-phenylalanyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 38) 3(RS)-(4-Methoxycarbonylphenyl)methoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 39) 3(RS)-[E-3-(4-Ethoxycarbonylphenyl)-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 40) 3(RS)-(2-Ethoxycarbonylphenyl)aminocarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 41) 3(RS)-4-[(4-Nitrophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 42) 3(RS)-Phenylmethoxycarbonyl-L-glutamyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide phenylmethyl ester; 43) 3S(or R)-(Tricyclo[3.3.1.1.sup.3,7]dec-1-yl)sulfonyl-L-valyl-N-[3-(1,1,1-

trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 44) 3(RS)-Phenylmethoxycarbonyl-L-[5-(phenylsulfonylamino)glutamyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 45) 3(RS)-[4-(Phenylsulfonylaminocarbonyl)phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 46) 3(RS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 47) 3(RS)-4-(1-Naphthylsulfonylamino)-1,4-dioxobutyl -L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 48) 3(RS)-[2-(4-Aminocarbonylphenoxy)-1-oxoethyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 49) 3(RS)-(4-Hydroxycarbonylphenyl)methoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 50) 3(RS)-[4-[4-(2-Amino-2-oxoethyl)phenoxy]-1-oxobutyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 51) 3(RS)-E-[3-(4-Hydroxycarbonylphenyl)-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 52) 3(RS)-[2-(4-Ethoxycarbonylphenoxy)-1-oxoethyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 53) 3(RS)-[3-(4-Ethoxycarbonylphenyl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 54) 3(RS)-4-Hydroxybenzoyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 55) 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 56) 3(RS)-[3-(4-Hydroxycarbonylphenyl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 57) 3(RS)-[3-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl]-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 58) 3(RS)-E-[3-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl]-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 59) 3(RS)-[1-[4-[[(4-Bromophenyl)sulfonyl][phenylmethyl]aminocarbonyl]phenyl]-1-oxomethyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 60) 3R(orS)-(Tricyclo[3.3.1.1.sup.3,7]dec-1-yl)sulfonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 61) 3S(orR)-[4-(Phenylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 62) 3S(or R)-Phenylmethoxycarbonyl-L-phenylglycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 63) 3S(or R)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 64) 3S(or R)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 65) 3S(or R)-Phenylmethoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 66) 3S(or R)-[(4-Carboxyphenyl)aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 67) 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 68) 3(RS)-N.sup.2,N.sup.6 -Di(phenylmethoxycarbonyl)-L-lysyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 69) 3(RS)-[1,4-Dioxo-4-(phenylsulfonylamino)butyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 70) 3(RS)-[4-(Methylsulfonylamino)-1,4-dioxobutyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 71) 3(RS)-N.sup.2 -[1,4-Dioxo-4-(phenylsulfonylamino)butyl]-N.sup.6 -phenylmethoxycarbonyl-L-lysyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; and 72) 3(RS)-[1,4-Dioxo-4-[(tricyclo[3.3.1.1.sup.3,7]dec-1-yl)sulfonylamino]butyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide.

. . . -[(phenylmethoxy)carbonyl]-L-lysyl-L-valyl-N-[3-(4-methyl-1,1,1-trifluoro-2-oxopentyl)]-L-prolinamide; 4) 3(RS)-[4-

(Methylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 5) 3(RS)-[4-(Phenylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 6) 3(RS)-(4-Hydroxycarbonylphenyl)aminocarbonyl-L-.alpha.-aminobutyryl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 7) 3(RS)-[Z-(4-Aminocarbonylamino-1,4-dioxo-2-butenyl)]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 8) 3(RS)-[[4-[(1-Naphthylsulfonyl)aminocarbonyl]phenyl]aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 9) 3(RS)-N.sup.2 -(4-Hydroxycarbonylphenyl)aminocarbonyl-N.sup.6 -phenylmethoxycarbonyl-L-lysyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 10) 3(RS)-(4-Hydroxycarbonylphenyl)carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 11) 3(RS)-(4-Hydroxycarbonylphenyl)aminocarbonyl-L-phenylalanyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 12) 3(RS)-4-[(4-Nitrophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 13) 3(RS)-Phenylmethoxycarbonyl-L-[5-(phenylsulfonylamino)glutamyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 14) 3(RS)-[4-(Phenylsulfonylaminocarbonyl)phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 15) 3(RS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 16) 3(RS)-4-(1-Naphthylsulfonylamino)-1,4-dioxobutyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 17) 3(RS)-(4-Hydroxycarbonylphenyl)methoxycarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 18) 3(RS)-E-[3-(4-Hydroxycarbonylphenyl)-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 19) 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 20) 3(RS)-[3-(4-Hydroxycarbonylphenyl)-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 21) 3(RS)-[3-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl]-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 22) 3(RS)-E-[3-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl]-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 23) 3S(orR)-[4-(Phenylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 24) 3S(or R)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 25) 3S(or R)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 26) 3S(or R)-[(4-Carboxyphenyl)aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 27) 3(RS)-[1,4-Dioxo-4-(phenylsulfonylamino)butyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; 28) 3(RS)-[4-(Methylsulfonylamino)-1,4-dioxobutyl]-L-leucyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; and 29) 3(RS)-N.sup.2 -[1,4-Dioxo-4-(phenylsulfonylamino)butyl]-N.sup.6 -phenylmethoxycarbonyl-L-lysyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide.

. . . of treating a warm-blooded animal having a tissue degenerative disease selected from the group consisting of pulmonary emphysema, atherosclerosis, rheumatoid **arthritis**, and osteo **arthritis**, which method comprises administering to said animal a leukocyte elastase inhibiting effective amount of a compound of claim 1.

. . . . animal having a disease condition mediated by human leukocyte elastase selected from the group consisting of pulmonary emphysema, atherosclerosis, rheumatoid **arthritis**, and osteo

arthritis, which method comprises administering to said animal a leukocyte elastase inhibiting effective amount of a compound of claim 1.

L2 ANSWER 11 OF 21 USPATFULL on STN

AB This invention relates to acylated enol derivatives of known elastase inhibitors. These compounds are useful in the treatment of various inflammatory diseases, including cystic fibrosis and emphysema or as prodrugs of compounds which are useful in the treatment of said diseases.

PI US 5698523 19971216 <--

SUMM . . . contributing to the tissue destruction associated with a number of inflammatory diseases such as chronic bronchitis, cystic fibrosis, and rheumatoid **arthritis**. J. L. Malech and J. I. Gallin, New Engl. J. Med., 317(11), 687 (1987). Elastase possesses a broad range of. . .

SUMM . . . anti-inflammatory effect useful in the treatment of emphysema, cystic fibrosis, adult respiratory distress syndrome, septicemia, disseminated intravascular coagulation, gout, rheumatoid **arthritis**, chronic bronchitis and inflammatory bowel disease; or are prodrugs of compounds which exhibit such effects.

DETD (E)-N-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[2-(acetyloxy)-3,3,3-trifluoro-1-(1-methylethyl)-1-propenyl]-L-prolinamide.

DETD . . . to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolyl, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . .

DETD Preparation of (E)-N-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[2-(acetyloxy)-3,3,3-trifluoro-1-(1-methylethyl)-1-propenyl]-L-prolinamide ##STR45##

DETD Method A; step a: N-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[3,3,3-trifluoro-1-(1-methylethyl)-2-oxopropyl]-L-prolinamide (54)

DETD To a stirred light suspension of 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoic acid (0.68 g, 2.02 mmol; EP Pat. Appl. Publ. No. 0189305 B1) in CH.sub.2 Cl.sub.2 (18 mL) and DMF (2. . .

DETD Step b: (E)-N-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[2-(acetyloxy)-3,3,3-trifluoro-1-(1-methylethyl)-1-propenyl]-L-prolinamide (MDL 105,928)

DETD . . . formula I will be particularly useful include: emphysema, cystic fibrosis, adult respiratory distress syndrome, septicemia, disseminated intravascular coagulation, gout, rheumatoid **arthritis**, chronic bronchitis and inflammatory bowel disease. Compounds of formula I which are particularly preferred for the treatment of neutrophil associated. . .

DETD (E)-N-[4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[2-(acetyloxy)-3,3,3-trifluoro-1-(1-methylethyl)-1-propenyl]-L-prolinamide.

DETD . . . elastase-mediated diseases including but not limited to emphysema, cystic fibrosis, adult rspiratory distress syndrome, septicemia, disseminated intravascular coagulation, gout, rheumatoid **arthritis**, chronic bronchitis and inflammatory bowel disease. However, it is understood that the present invention is not limited by any particular. . .

L2 ANSWER 12 OF 21 USPATFULL on STN

AB The invention concerns pharmaceutically useful trifluoromethyl ketone substituted di-, tri- and tetra-peptide derivatives of the formulae Ia, Ib, Ic set out hereinafter, and salts thereof, which are inhibitors of

human leukocyte elastase. Also described herein are pharmaceutical compositions containing a peptide derivative and processes and intermediates for use in the manufacture of the peptide derivatives.

PI US 5414132 19950509 <--

SUMM . . . in pharmacological, diagnostic and related studies and in the treatment of tissue degenerative diseases such as pulmonary emphysema, atherosclerosis, rheumatoid **arthritis** and osteo **arthritis** in warm blooded animals. The invention also includes intermediates useful in the synthesis of these peptide derivatives, processes for preparing. . .

SUMM (x) acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsufonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . by a member selected from carboxy, alkoxycarbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . .

SUMM . . . a member selected from carboxy, alkoxycarbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . .

SUMM (x) acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons), and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing from 1 to 15 carbons, and provided that when the acylsulfonamido contains an aryl the aryl may be further. . .

SUMM . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . alkylcarbonylamino wherein the alkyl group contains 1 to 6

carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons (e.g., 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl or 4-[(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl);

SUMM (x) ethyl substituted by an acylsulfonamido selected from the group consisting of 2-(methylsulfonylaminocarbonyl)ethyl, 2-(phenylsulfonylaminocarbonyl)ethyl, 2-[(1-adamantyl)**sulfonylaminocarbonyl**]ethyl, and 2-[(1-naphthyl)**sulfonylaminocarbonyl**]ethyl;

SUMM . . . carboxy, methoxy, ethoxy, methoxycarbonyl, ethoxycarbonyl, methylcarbonylamino, an acylsulfonamido containing 2 carbons, (e.g., 4-(methylsulfonaminocarbonyl)phenyl), an acylsulfonamido containing 7 carbons (e.g., 4-(phenylsulfonylaminocarbonyl)phenyl, 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl, or [(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl), an acylsulfonamido containing 11 carbons (e.g., 4(1-naphthylsulfonylaminocarbonylphenyl), an acylsulfonamido containing 14 carbons (e.g., 4-(4-bromophenylsulfonylamino(benzyl)carbonyl)phenyl); and an aryl group containing 6. . .

SUMM . . . an ethenyl group substituted by a member s elected from the group consisting of carboxy, ethoxycarbonyl, ureidocarbonyl (e.g., Z-2-(aminocarbonylamino)ethenyl)), acylsulfonamidophenyl (e.g.,2-[4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl]ethenyl), and 4-carboxyphenyl (e.g., E-2-(4-carboxyphenyl)ethenyl;

SUMM . . . to a warm-blooded animal in need thereof, particularly a human, for the treatment of conditions of pulmonary emphysema, atherosclerosis, rheumatoid **arthritis**, and osteo **arthritis**, in particular for emphysema. The mode of administration may be oral, parenteral, including the subcutaneous deposit by means of an. . .

DETD 3(RS)-4-[(4-Nitrophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 .dbd.CH(CH.sub.3)CH.sub.3, R.sup.2 .dbd.(CH.sub.3).sub.2 CH--, R.sup.3 .dbd.4-[(4-NO.sub.2 .phi.)S(O.sub.2)NHCO].phi., R.sup.4 .dbd.H, A.dbd.CO, n=1)

DETD 3(RS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 .dbd.CH(CH.sub.3)CH.sub.3, R.sup.2 .dbd.(CH.sub.3).sub.2 CH--, R.sup.3 .dbd.4-[(4-Br.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 .dbd.H, A.dbd.CO, n=1)

DETD b. 3(RS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 .dbd.CH(CH.sub.3)CH.sub.3, R.sup.2 .dbd.(CH.sub.3).sub.2 CH--, R.sup.3 .dbd.4-[(4-Br-.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 .dbd.H, A.dbd.CO, n=1)

DETD 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 .dbd.CH(CH.sub.3)CH.sub.3, R.sup.2 .dbd.(CH.sub.3).sub.2 CH, R.sup.3 .dbd.4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi.--, R.sup.4 .dbd.H, A.dbd.CO, n=1)

DETD 3(RS)-[3-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl]-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 .dbd.CH(CH.sub.3)CH.sub.3, R.sup.2 .dbd.(CH.sub.3).sub.2 CH--, R.sup.3 .dbd.4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi.(CH.sub.2).sub.2, R.sup.4 .dbd.H, A.dbd.CO, n=1)

DETD 3(RS)-E-[3-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl]-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 .dbd.CH(CH.sub.3)CH.sub.3, R.sup.2 .dbd.(CH.sub.3).sub.2 CH--, R.sup.3 .dbd.E-[4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi.--CH.dbd.CH--, R.sup.4 .dbd.H, A.dbd.CO, n=1)

DETD 3R(orS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**

]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxo-pentyl)]-L-prolinamide (Formula Ib, R.sup.1 .dbd.CH(CH.sub.3)CH.sub.3,R.sup.2 .dbd.(CH.sub.3).sub.2 CH--, R.sup.3 .dbd.4-[4-(Br.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 .dbd.H, A.dbd.CO, n=1)

DETD 3S (or R)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 .dbd.CH(CH.sub.3)CH.sub.3, R.sup.2 .dbd.(CH.sub.3).sub.2 CH--, R.sup.3 .dbd.4-[(4-Br.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 .dbd.H, A.dbd.CO, n=1)

DETD 3S(or R)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 .dbd.CH(CH.sub.3)CH.sub.3, R.sup.2 .dbd.(CH.sub.3).sub.2 CH--, R.sup.3 .dbd.4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 .dbd.H, A.dbd.CO, n=1)

DETD 3R(or S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl]carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 .dbd.CH(CH.sub.3)CH.sub.3, R.sup.2 .dbd.(CH.sub.3).sub.2 CH--, R.sup.3 .dbd.4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 .dbd.H, A.dbd.CO, n=1)

DETD 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 .dbd.CH(CH.sub.3)CH.sub.3, R.sup.2 .dbd.CH(CH.sub.3)CH.sub.3, R.sup.3 .dbd.4-[(4-Cl.phi.)S(O.sub.2)NHCO].phi., R.sup.4 .dbd.H, A.dbd.CO, n=1)

DETD a. 1,1-Dimethylethyl 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoate

DETD b. 4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzenecarboxylic acid

DETD c. 2(RS),3(SR)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R.sup.1 .dbd.CH(CH.sub.3)CH.sub.3, R.sup.2 .dbd.CH(CH.sub.3)CH.sub.3, R.sup.3 .dbd.4-[(4Cl-.phi.)S(O.sub.2)NHCO].phi., R.sup.4 .dbd.H, A.dbd.CO, n=1)

DETD d. 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 .dbd.CH(CH.sub.3)CH.sub.3, R.sup.2 .dbd.CH(CH.sub.3)CH.sub.3 , R.sup.3 .dbd.4-[(4-Cl.phi.)S(O.sub.2)NHCO].phi., R.sup.4 .dbd.H, A.dbd.CO, n=1)

L2 ANSWER 13 OF 21 USPATFULL on STN

AB Tetrahydroisoquinoline amides having the general structure ##STR1## are disclosed, the substituents defined hereinbelow, which amides are useful in inhibiting human leukocyte and neutrophil elastaes.

PI US 5232928 19930803 <--

DETD . . . treatment of tissue degenerative diseases. Additionally, such inhibitors could be used in the diagnosis and treatment of pulmonary emphysema, rheumatoid **arthritis**, osteoarthritis, and arteriosclerosis, among other diseases. The substituted amides of the present invention may be represented by the following formulae:. . .

DETD . . . the present invention would be useful in the diagnosis and treatment of tissue degenerative diseases such as pulmonary emphysema, rheumatoid **arthritis**, adult respiratory distress syndrome - otherosclerosis, osteo **arthritis**, chronic obstructive lung disease, glomerular nephritis, inter alia.

DETD . . . administered for the alleviation of conditions which include tissue degenerative diseases such as: pulmonary emphysema, artherosclerosis and osteo- and rheumatoid **arthritis**, in particular emphysema, and other diseases. The mode of administration may be parenteral, including the subcutaneous deposit of an osmotic. . .

DETD N-[3-(R,S)-[2-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl]-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]carbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-

oxopentyl)]amine

DETD N-[3-(R,S)-[2-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl-L-valyl]-(6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolyl)]carbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amine

DETD N-[3'-(R,S)-[2'-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-leucyl]-spiro[cyclopentane-1,1'-(6.7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]]-carbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amine

DETD N-[3-(R,S)-[2-[4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl]-3-methyl -1,2,3,4-tetrahydroisoquinolyl)]carbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amine

DETD N-[3-(R,S)-[2-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl]-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]carbonyl]-N-[3-(1,1-difluoro-2-oxo-4-methyl-1-aminocarbonylpentyl)]

DETD N-[3-(R,S)-[2-[4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl]-(1,2,3,4-tetrahydroisoquinolyl)]carbonyl]-N-[3-(1,1-difluoro-2-oxo-4-methyl-1-carboxyl-pentyl)]

DETD 1,1-Dimethylethyl-4-](4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoate

DETD . . . over MgSO.sub.4 followed by filtration and evaporation a solid was obtaind which was treated with ether and filtered to yield 1,1-dimethylethyl-4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoate (5.8 g, 42.3%) as a white solid (mp: above 300.degree. C.) which was used for hydrolysis.

DETD 4-](4-Chlorophenyl)**sulfonylaminocarbonyl**]benzene carboxylic acid

DETD . . . before being filtered, washed with water and dried to yield a white solid. Recrystallization from ethanol/water (1:1) gave the product 4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**] benzene carboxylic acid in 63% yield melting at 285.degree.-287.degree. C.

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-hydroxypentyl)]1,2,3,4-tetrahydro-3-isoquinolinecarboxamide

DETD . . . stated order in dry THF (35 mL) at 0.degree.-5.degree. C. L-Valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-hydroxypentyl)]-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide (0.52 g, 1.21 mmol), HOBT (0.15 g, 1.1 mmol), 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzene carboxylic acid (0.37 g, 1.1 mmol), and WSCDI (0.45 g, 1.21 mmol). The mixture was stirred at 0.degree.-5.degree. C. for. . .

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-1,2,3,4-tetrahydro-3-isoquinoline-carboxamide.

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-hydroxypentyl)]-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide (0.33 g, 0.44 mmol) was added to CH.sub.2 Cl.sub.2 (15mL) followed by Dess-Martin periodinane (0.56 g, 1.3 mmol) in CH.sub.2. . .

CLM What is claimed is:

3. A compound selected from the group consisting of:

N-[3-(R,S)-[2-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl]-(6,7-dimethoxy -1,2,3,4-tetrahydro-isoquinolyl)carbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amine

N-[3-(R,S)-[2-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl-L-valyl]-(6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolyl)]carbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amine

N-[3-[2-[2-Amino-.alpha.-(methoxyimino)-4-thiazoleacetyl-L-valyl]-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]carbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amine

N-[3-[2-[2-Amino-.alpha.-(carboxymethoxyimino)-4-thiazolacetyl-L-valyl]-(5,6,7-trimethoxy-1,2,3,4-

tetrahydroisoquinolyl)]carbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amine N-[3-(R,S)-[2-[4-[(4-Bromophenyl) **sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl]-(6,7-dimethoxy -1,1-dimethyl-1,2,3,4-tetrahydroisoquinolyl)]carbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amine N-[3'-(R,S)-[2'-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-leucyl]-spiro [cyclopentane-1,1'-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]-carbonyl]-N-[3(1,1,1-trifluoro -4-methyl-2-oxopentyl)]amine N-[3-(R,S)-[2-[4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-leucyl]-(1-benzyl -5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinolyl)]-carbonyl]-N-(3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amine N-[3'-(R,S)-[2'-[2-Amino-.alpha.-(methoxyimino)-4-thiazolacetyl-L-valyl]-spiro[cyclohexane -1,1'-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]carbonyl]-N-[3-(1,1,1-trifluoro-4-methyl -2-oxopentyl)]amine N-[3'-(R,S)-[2'-[2-(methoxysuccinyl)amino-.alpha.-(methoxyimino)-4-thiazolacetyl-L-valyl(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]carbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amine N-[3-(R,S)-[2-[4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl]-3-methyl -1,2,3,4-tetrahydroisoquinolyl)]carbonyl]-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amine N-[3-(R,S)-[2-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl]-(6,7-dimethoxy -1,2,3,4-tetrahydroisoquinolyl)]carbonyl]-N-[3-(1,1-difluoro-2-oxo-4-methyl-1-aminocarbonylpentyl)] N-[3-(R,S)-[2-[4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl]-(1,2,3,4-tetrahydroisoquinolyl)]carbonyl]-N-[3-(1,1,-difluoro-2-oxo-4-methyl-1-carboxyl-pentyl)] N-[3'-(R,S)-[2'-[(2-methoxysuccinyl)amino-.alpha.-(methoxycarboxy)-4-thiazole-acetyl)-L-valyl]-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]carbonyl]-N-[3-(1,1-difluoro-2-oxo-4-methyl-1-aminocarbonylpentyl)] N-[.alpha.-(methoxyimino)-2-furylacetyl-L-valyl]-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]carbonyl]-N -[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amine

L2 ANSWER 14 OF 21 USPATFULL on STN

AB N-substituted amides which inhibit hydrolysis of elastin, are described, which compounds are tri-and di- fluoromethyl ketone amide and non-naturally occurring n-substituted amino acids derivatives.

PI US 5221665 19930622 <--

DETD . . . may serve as diagnostic aids. Accordingly, such inhibitors could be used in the diagnosis and treatment of pulmonary emphysema, rheumatoid **arthritis**, osteoarthritis, and arteriosclerosis, among other diseases.

DETD . . . the present invention would be useful in the diagnosis and treatment of tissue degenerative diseases such as pulmonary emphysema, rheumatoid **arthritis**, adult respiratory distress syndrome, otherosclerosis, osteo **arthritis**, chronic obstructive lung disease, glomerular nephritis, inter alia.

DETD . . . administered for the alleviation of conditions which include tissue degenerative diseases such as: pulmonary emphysema, arteriosclerosis and osteo- and rheumatoid **arthritis**, especially emphysema. The mode of administration may be parenteral, oral, intravenous, as a powder or liquid aerosol, or subcutaneous by. . .

DETD [[4-(4-Bromophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-(n-hexyl)glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-(phenyl)glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-(4-trifluoromethylphenyl)glycyl-N-[3-(1,

1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-(3,4-dimethoxyphenyl)glycyl-N-[3-(1, 1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Bromophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-(N-methyl) valyl-N-(2,3-dihydro-1H-inden-1-yl) glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-[2-(3-indolyl)ethyl]glycyl-N-[3-(1, 1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-(N-cyclopentyl)valyl-N-(benzimidazo-2-yl) glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Bromophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-[(N-ethoxycarbonyl)piperidin-4-yl)]glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amide [2-Amino-.alpha.-(methoxyimino)-4-thiazoleacetyl]-L-valyl-N-(2, 3-dihydro-1H-inden-5-yl)glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-[1-[2-(morpholin-4-yl)]ethyl]glycyl-N-[3-(1, 1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-leucyl-N-[1-[2-(pyrid-2-yl)]ethyl]-L-alanyl-N-[3-(1, 1,1-trifluoro-4-m ethyl-2-oxopentyl)]amide

DETD [[4-(4-Bromophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-(2-indanylmethyl)glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-(piperidin-1-yl)glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-[1-[3-(pyrrolidin-2-one)-1-yl]propyl] glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Phenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl-L-valyl-N-[(tetrahydro-2H-pyran-2-yl)methyl]glycyl-N-[3-(1, 1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-leucyl-N-(quinuclidin-3-yl)glycyl-N-[3-(1, 1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-[(cyclohexyl)methyl]glycyl-N-[3-(1, 1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-[(2-pyrrole)methyl]glycyl-N-[3-(1, 1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(Bromophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-(5,6-dimethoxy-2,3-dihydro-1H-inden-2-yl) glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Bromophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-[L-2-oxohexamethyleneimine-3-yl)]glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Bromophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-(6,7,8,9-tetrahydro-5H-benzocyclohepten-7-yl) glycyl-N-[3-(1, 1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Bromophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-(5H-benzoimidazol-6-yl)glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]amide

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-(2,3-dihydro-1H-inden-2-yl)glycyl-N-[3-(1,1,1-trifluoro-4-(3,4-methylenedioxy) phenyl-2-oxobutyl)]amide

DETD [[4-(4-Bromophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl)]-L-valyl-N-(3-carboxypropyl)glycyl-N-[3-(1, 1,1-trifluoro-4-(3,4,5-

trimethoxy)phenyl-2-oxobutyl)]amide

DETD 1,1-Dimethylethyl-4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**] benzoate

DETD . . . over MgSO.sub.4 followed by filtration and evaporation a solid was obtained which was treated with ether and filtered to yield 1,1-dimethylethyl-4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoate (5.8 g, 42.3%) as a white solid (mp: above 300.degree. C.) which was used for hydrolysis. 4-[(4-Chlorophenyl) **sulfonylaminocarbonyl** benzene carboxylic acid

DETD . . . before being filtered, washed with water and dried to yield a white solid. Recrystallization from ethanol/water (1:1) gave the product 4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**] benzene carboxylic acid in 63% yield melting at 285.degree.-287.degree. C.

DETD [4-(4-Chlorophenyl)**sulfonylaminocarbonyl** phenyl-1-oxomethyl]-L-Valyl-N-2-(3,4-dimethoxy)phenethyl]-glycyl-N-3-(1, 1,1-trifluoro-4-methyl-2-hydroxypentyl)] amide

DETD . . . in dry THF (35 mL) at 0.degree.-5.degree. C.: L-Valyl-N-[2-(3,4-dimethoxy)phenethyl]glycyl-N-[3-(1, 1,1-trifluoro-4-methyl-2-hydroxypentyl]amide (0.8 g, 1.63 mmol), hydroxybenzotriazole (HOBT), 0.2 g, 1.48 mmol), 4-[(4-chlorophenyl)-**sulfonylaminocarbonyl**]benzene carboxylic acid (0.5 g, 1.48 mmol), WSCDI (0.312 g, 1.63 mmol) and triethylamine (0.165 g, 1.63 mmol). The mixture was. . .

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-Valyl-N-[2-(3,4-dimethoxy)phenethyl] glycyl-N-[3-(1,1,1-trifluoro-4-methyl- 2-hydroxypentyl)] amide (0.4 g, 0.492 mmol) was added to THF (20 mL) followed by Dess-Martin periodinane (0.42 g,. . .

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl** phenyl-1-oxomethyl 1-L-Valyl-N-(2-indanyl)glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-hydroxypentyl)]amide

DETD . . . following reactants were mixed in the stated order in L-valyl-N-(2-indanyl)glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-hydroxypentyl)]amide (1.3 g, 2.93 mmol), hydroxybenzotriazole (HOBT), (0.36 g, 2.66 mmol), 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzene carboxylic acid (0.9 g, 2.64 mmol) and WSCDI (0.56 g, 2.92 mmol). The mixture was stirred at 0.degree.-5.degree. C. for. . .

DETD [4-(4-Chlorophenyl)**sulfonylaminocarbonyl** phenyl-1-oxomethyl]-L-valyl-N-(2-indanyl)glycyl-N-3-(1,1,1-trifluoro-4-methyl-2-oxypentyl)1amide

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-(2-indanyl)glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-hydroxypentyl)]amide (1.6 g, 2.1 mmol) was added to THF (25 mL) followed by Dess-Martin periodinane (2.66 g, 6.3 mmol). . .

DETD [4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl -L-Valyl-N-(exo-bicyclo2. 2.1]hept-2-yl) glycyl-N-3-(1,1,1-trifluoro-4-methyl-2-hydroxy-pentyl)]amide.

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-Valyl-N-(exo-bicyclo[2,2,1]hept-2-yl)-glycyl-N-[3-(1, 1,1-trifluoro-4-methyl-2-oxypentyl)] amide.

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-valyl-N-(exo-bicyclo[2.2.1]hept-2-yl)-glycyl-N-[3-(1, 1,1-trifluoro-4-methyl-2-hydroxy-pentyl)]amide (0.6 g, 0.807 mmol) was added to CH.sub.2 Cl.sub.2 (20 mL) followed by Dess-Martin periodinane (0.69 g,. . .

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl** phenyl-1-oxomethyl]-L-Valyl-N-(cyclopentyl)glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-hydroxypentyl)amide]

DETD (4-(4-Chlorophenyl)**sulfonylaminocarbonyl** phenyl-1-oxomethyl]-L-Valyl-N-cyclopentyl-glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxypentyl)1amide

DETD [[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl-1-oxomethyl]-L-Valyl-N-(cyclopentyl)glycyl-N-[3-(1,1,1-trifluoro-4-methyl-2-hydroxy

pentyl)]amide (0.72 g, 1.0 mmol) was added to THF (20 mL) followed by Dess-Martin periodinane (1.27 g, 3.0 mmol). . .

L2 ANSWER 15 OF 21 USPATFULL on STN

AB The invention concerns pharmaceutically useful trifluoromethyl ketone substituted di-, tri- and tetra-peptide derivatives of the formulae Ia, Ib, Ic set out hereinafter, and salts thereof, which are inhibitors of human leukocyte elastase. Also described herein are pharmaceutical compositions containing a peptide derivative and processes and intermediates for use in the manufacture of the peptide derivatives.

PI US 5194588 19930316 <--

SUMM . . . in pharmacological, diagnostic and related studies and in the treatment of tissue degenerative diseases such as pulmonary emphysema, atherosclerosis, rheumatoid **arthritis** and osteo **arthritis** in warm blooded animals. The invention also includes intermediates useful in the synthesis of these peptide derivatives, processes for preparing. . .

SUMM (x) acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . by a member selected from carboxy, alkoxycarbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . .

SUMM . . . a member selected from carboxy, alkoxycarbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . .

SUMM (x) acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons), and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing from 1 to 15 carbons, and provided that when the acylsulfonamido contains an

aryl the aryl may be further. . .

SUMM . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons (e.g., 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl or 4-[(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl);

SUMM (x) ethyl substituted by an acylsulfonamido selected from the group consisting of 2-(methylsulfonylaminocarbonyl)ethyl, 2-(phenylsulfonylaminocarbonyl)ethyl, 2-[(1-adamantyl)**sulfonylaminocarbonyl**]ethyl, and 2-[(1-naphthyl)**sulfonylaminocarbonyl**]ethyl;

SUMM . . . carboxy, methoxy, ethoxy, methoxycarbonyl, ethoxycarbonyl, methylcarbonylamino, an acylsulfonamido containing 2 carbons, (e.g., 4-(methylsulfonaminocarbonyl)phenyl), an acylsulfonamido containing 7 carbons (e.g., 4-(phenylsulfonylaminocarbonyl)phenyl, 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl, or [(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl), an acylsulfonamido containing 11 carbons (e.g., 4(1-naphthylsulfonylaminocarbonylphenyl), an acylsulfonamido containing 14 carbons (e.g., 4-(4-bromophenylsulfonylamino(benzyl)carbonyl)phenyl); and an aryl group containing 6. . .

SUMM . . . an ethenyl group substituted by a member selected from the group consisting of carboxy, ethoxycarbonyl, ureidocarbonyl (e.g., Z-2-(aminocarbonylamino)ethenyl)), acylsulfonamidophenyl (e.g., 2-[4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl]-ethenyl), and 4-carboxyphenyl (e.g., E-2-(4-carboxyphenyl)ethenyl;

SUMM . . . to a warm-blooded animal in need thereof, particularly a human, for the treatment of conditions of pulmonary emphysema, atherosclerosis, rheumatoid **arthritis**, and osteo **arthritis**, in particular for emphysema. The mode of administration may be oral, parenteral, including the subcutaneous deposit by means of an. . .

DETD 3(RS)-4-[(4-Nitrophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-NO.sub.2 .phi.)S(O.sub.2)NHCO].phi., R.sup.4 =H, A=Co, n=1)

DETD 3(RS)-[4-[4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Br.phi.)S(O.sub.2)NHC(O)].phi., R.sup.2 =H, A=CO, n=1)

DETD b. 3(RS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Br-.phi.)S(O.sub.2) NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopenyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi.--, R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-[3-[4-(4-Chlorophenyl)**sulfonylaminocarbonyl**]-phenyl]-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi.(CH.sub.2).sub.2, R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-E-[3-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]-phenyl]-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-

oxopenyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =E-[4-[4-(4-Cl.phi.)S(O.sub.2)NHC(O)].phi.--CH.dbd.CH--, R.sup.4 =H, A=CO, n=1)

DETD 3R(orS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxo-pentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[4-(Br.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD 3S(or R)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Br.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD 3S(or R)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD 3R(or S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]-phenyl]carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =CH(CH.sub.3)CH.sub.3, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHCO].phi., R.sup.4 =H, A=CO, n=1)

DETD a. 1,1-Dimethylethyl 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoate

DETD b. 4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzenecarboxylic acid

DETD c. 2(RS),3(SR)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =CH(CH.sub.3)CH.sub.3, R.sup.3 =4-[(4Cl-.phi.)S(O.sub.2)NHCO].phi., R.sup.4 =H, A=CO, n=1)

DETD d. 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =CH(CH.sub.3)CH.sub.3, R.sup.3 =4-[(3-Cl.phi.)S(O.sub.2)NHCO].phi., R.sup.4 =H, A=CO, n=1)

CLM What is claimed is:

. . . to 13 carbons; (w) arylsulfonamido wherein the aryl group contains 6, 10 or 12 carbons; (x) acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal portion of the acylsulfonamide. . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsufamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

. . . to 13 carbons; (w) arylsulfonamido wherein the aryl group contains 6, 10 or 12 carbons; (x) acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal portion of the acylsulfonamide. . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsufamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

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AB The invention provides a series of novel heterocyclic ketones of formula I ##STR1## and pharmaceutically acceptable base-addition salts thereof, in which the values of R.sup.4, L, A, X and Q have the meanings defined in the following specification. The compounds of formula I are inhibitors of human leukocytic elastase. The invention also provides pharmaceutical compositions containing a compound of formula I, or a pharmaceutically acceptable base-addition salt thereof, and processes and intermediates for the manufacture of compounds of formula I.

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SUMM The activity of proteolytic enzymes of the elastase type has been implicated in several pathological conditions, for example in **arthritis** and in pulmonary emphysema. Pharmacological inhibition of an elastase enzyme would be expected to prevent or ameliorate an associated pathological. . .

SUMM (i) [4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-(5-hydroxybenzoxazol-2-yl)carbonyl-2-methylpropyl]-L-prolinamide:

SUMM (ii) [4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-[5-(aminocarbonyl)benzoxazol-2-yl)carbonyl-2-methylpropyl]-L-prolinamide; and

SUMM (iii) [4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-[5-(hydroxymethyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide.

DETD (S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=2-benzoxazolyl, A=CO, L=p-phenylene, R.sup.4 =R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 =4--ClC.sub.6 H.sub.4).

DETD 1. [4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula III, heterocycle containing X, N and Q=2-benzoxazolyl, A=CO, L=p-phenylene, R.sup.4 =R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 =4--ClC.sub.6 H.sub.4).

DETD 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (710 mg) was added to a solution of the product of Example 1k (1.38g), 1-hydroxybenzotriazole (983 mg) and 4-(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoic acid (see parts n and o below) (1.12 g) in tetrahydrofuran (18 ml): and the solution was stirred at room. . .

DETD m. (S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=2-benzoxazolyl, A=CO, L=p-phenylene, R.sup.4 =R5.S(O.sub.2).NH.CO--, R.sup.5 =4--ClC.sub.6 H.sub.4)

DETD n. 1,1-Dimethylethyl 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoate

DETD o. 4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoic acid

DETD (S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl[-L-valyl-N-[1-(5-methoxybenzoxazol-2-yl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=5-methoxybenzoxazol-2-yl, A=CO, L=p-phenylene, R.sup.4 =R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 =4--ClC.sub.6 H.sub.4)

DETD f. (1S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-(hydroxy)(5-methoxybenzoxazol-2-yl)methyl-2-methylpropyl]-L-prolinamide (Formula III, heterocycle containing X, N and Q=5-methoxybenzoxazol-2-yl, A=CO, L=p-phenylene, R.sup.4 =R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 =4--ClC.sub.6 H.sub.4)

DETD g. (S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-(5-methoxybenzoxazol-2-yl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=5-methoxybenzoxazol-2-yl, A=CO, L=p-phenylene, R.sup.4 =R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 =4--ClC.sub.6 H.sub.4)

DETD (S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**
]benzoyl]-L-valyl-N-[1-(5-hydroxybenzoxazol-2-yl)carbonyl2-methylpropyl]-
L-prolinamide (Formula I, heterocycle containing X, N and
Q=5-hydroxybenzoxazol-2-yl, A=CO, L=p-phenylene, R.sup.4
=R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 =4--ClC.sub.6 H.sub.4)

DETD [4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-
[1-[5-(aminocarbonyl)benzoxazol-2-yl)carbonyl-2-methylpropyl]-L-
prolinamide (Formula I, heterocycle containing X, N and
Q=5-(aminocarbonyl)benzoxazol-2-yl, A=CO, L=p-phenylene, R.sup.4
=R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 =4-ClC.sub.6 H.sub.4)

DETD d. (1S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**
]benzoyl]-L-valyl-N-[1-[5-(aminocarbonyl)benzoxazol-2-yl]hydroxymethyl-2-
methylpropyl]-L-prolinamide (Formula III, heterocycle containing X, N
and Q=5-(aminocarbonyl)benzoxazol-2-yl, A=CO, L=p-phenylene, R.sup.4
=R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 =4--ClC.sub.6 H.sub.4)

DETD e. [4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**
]benzoyl]-L-valyl-N-1-(5-(aminocarbonyl)benzoxazol-2-yl)carbonyl-2-
methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and
Q=5-(aminocarbonyl)benzoxazol-2-yl, A=CO, L=p-phenylene, R.sup.4
=R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 =4--ClC.sub.6 H.sub.4)

DETD [4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-
[1-[5-(hydroxymethyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-
prolinamide (Formula I, heterocycle containing X, N and
Q=5-(hydroxymethyl)benzoxazol-2-yl, A=CO, L=p-phenylene, R.sup.4
=R.sup.5.S(O.sub.2).--NH.CO--, R.sup.5 =4--ClC.sup.6 H.sup.4)

DETD f. [4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**
]benzoyl]-L-valyl-N-[1-[5-(hydroxymethyl)benzoxazol-2-yl]carbonyl-2-
methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and
Q=5-(hydroxymethyl)benzoxazol-2-yl, A=CO, L=p-phenylene, R.sup.4
=R.sup.5.S(O.sub.2).--NH.CO--, R.sup.5 =r--ClC.sub.6 H.sub.4)

DETD (S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**
]benzoyl]-L-valyl-N-[1-[5-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-
methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and
Q.dbd.5-(methoxycarbonyl)benzoxazol-2-yl, A.dbd.CO, L.dbd.p-phenylene,
R.sup.4 .dbd.R.sup.5.S(O.sub.2).NH.--CO--, R.sup.5 .dbd.4--ClC.sub.6
H.sub.4)

DETD d. (S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**
]benzoyl]-L-valyl-N-[1-[5-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-
methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and
Q.dbd.5-(methoxycarbonyl)benzoxazol-2-yl, A.dbd.CO, L.dbd.p-phenylene,
R.sup.4 .dbd.R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 .dbd.4--ClC.sub.6
H.sub.4)

DETD (S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**
]benzoyl]-L-valyl-N-[1-[6-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-
methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and
Q.dbd.6-(methoxycarbonyl)ol-2-yl, benzoxazol-2-yl, A.dbd.CO,
L.dbd.p-phenylene, R.sup.4 .dbd.R.sup.5.S(O.sub.2).NH.CO--, R.sup.5
.dbd.4--ClC.sub.6 H.sub.4)

DETD d. (S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**
]benzoyl]-L-valyl-N-[1-[6-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-
methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and
Q.dbd.6-(methoxycarbonyl)benzoxazol-2-yl, A.dbd.CO, L.dbd.p-phenylene,
R.sup.4 .dbd.R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 .dbd.4--ClC.sub.6
H.sub.4)

DETD 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (75 mg) was
added to a solution of the product of Example 9c, above,
1-hydroxybenzotriazole (50 mg) and 4-[(4-chlorophenyl)
sulfonylaminocarbonyl]benzoic acid (130 mg) in methylene
chloride (2 ml) and tetrahydrofuran (2 ml) followed by the addition of
4-methylmorpholine (0.041 ml). . .

DETD (S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**
]benzoyl-L-valyl-N-[1-(5-carboxybenzoxazol-2yl)carbonyl-2-methylpropyl]-

L-prolinamide (Formula I, heterocycle containing X, N and Q.dbd.5-carboxybenzoxazol-2-yl, A.dbd.CO, L.dbd.p-phenylene, R.sup.4 .dbd.R.sup.5.S(O).NH.CO--, R.sup.5 .dbd.4--ClC.sub.6 H.sub.4)

DETD c. (1S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-(5-carboxybenzoxazol-2-yl)hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula III, heterocycle containing X, N and Q.dbd.5-carboxybenzoxazol-2-yl, A.dbd.CO, L.dbd.p-phenylene, R.sup.4 .dbd.R.sup.5.S(O.sub.2) NH.CO--, R.sup.5 .dbd.4--ClC.sub.6 H.sub.4)

DETD Isobutyl chloroformate (0.34 ml) was added dropwise over the course of three min to a stirred, -40.degree. solution of 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoic acid (850 mg) and 4-methylmorpholine (0.58 ml) in dry tetrahydrofuran (12 ml). The mixture was stirred for 30 min after. . .

DETD d. (S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl-L-valyl-N-[1-(5-carboxybenzoxazol-2-yl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q.dbd.5-carboxybenzoxazol-2-yl, A.dbd.CO, L.dbd.p-phenylene, R.sup.4 .dbd.R.sup.5.S(O.sub.2).-NH.CO--, R.sup.5 .dbd.4--ClC.sub.6 H.sub.4)

DETD [4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-(2-oxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q.dbd.2-oxazolyl, A.dbd.CO, L.dbd.p-phenylene, R.sup.4 .dbd.R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 .dbd.4--ClC.sub.6 H.sub.4)

DETD d. [4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl-L-valyl-N-[1-(2-oxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q.dbd.2-oxazolyl, L.dbd.p-phenylene, R.sup.4 .dbd.R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 .dbd.4--ClC.sub.6 H.sub.4)

DETD . . . high vacuum for 20 min. The residue was dissolved in tetrahydrofuran (40 ml) and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (429 mg), 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoic acid (800 mg) and 4-dimethylaminopyridine (1.97 g). The mixture was stirred at room temperature for 16 hr, dissolved in ethyl. . .

DETD [4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-(2-benzothiazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q.dbd.2-benzothiazolyl, A.dbd.CO, L.dbd.p-phenylene, R.sup.4 .dbd.R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 .dbd.4--ClC.sub.6 H.sub.4)

DETD f. [4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-(2-benzothiazolyl)carbonyl-2-methyl-propyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q.dbd.2-benzothiazolyl, A.dbd.CO, L.dbd.p-phenylene, R.sup.4 .dbd.R.sup.5.S(O).NH.CO--, R.sup.5 .dbd.4--ClC.sub.6 H.sub.4)

DETD Amine prepared according to the procedure of Example 13e and used without further purification (0.34 g), 1-hydroxybenzotriazole (0.21 g) and 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoic acid (0.27 g) were combined in dichloromethane (12 ml) and the suspension was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.17 g). Stirring. . .

DETD (S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[2-methyl-1-(2-thiazolyl)carbonylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q.dbd.2-thiazolyl, A.dbd.CO, L.dbd.p-phenylene, R.sup.4 .dbd.R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 .dbd.4--ClC.sub.6 H.sub.4)

DETD e. (S)-[4[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[2-methyl-1-(2-thiazolyl)carbonylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q.dbd.2-thiazolyl, A.dbd.CO, L.dbd.p-phenylene, R.sup.4 .dbd.R.sup.5.(SO.sub.2).NH.CO--, R.sup.5 .dbd.4--ClC.sub.6 H.sub.4)

DETD . . . amino ketone prepared according to the procedure of Example 14d and used without further purification (1.14 g), 1-hydroxybenzotriazole

(0.13 g), 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoic acid (0.34 g) and 4-methylmorpholine (0.59 ml) were dissolved in tetrahydrofuran and the mixture was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The. . .

DETD S-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-[5-(aminocarbonyl)benzoxazol-2-yl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q.dbd.5-(aminocarbonyl)benzoxazol-2-yl, A.dbd.CO, L.dbd.p-phenylene, R.sup.4 .dbd.R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 .dbd.4--ClC.sub.6 H.sub.4)

DETD c. [4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-L-proline t-butyl ester

DETD 4-Dimethylaminopyridine (16.4 g) was added to a solution of 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoic acid (45.6 g) in methylene chloride (250 ml). The mixture was stirred 15 min before amine from Example 19b (39.9. . . chromatographed, eluting with methanol:methylene chloride (gradient: 0:1 (1.5 liter), 2:98 (1.5 liter), 4:96 (1.5 liter), 5:95 (4 liter)), to afford [4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-L-proline t-butyl ester (65.5 g, 73%) as a white foam; TLC, R.sub.f .dbd.0.50, methanol:dichloromethane:acetic acid (2:98:1).

DETD d. [4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-L-proline (Formula IXa, A.dbd.CO, L.dbd.p-phenylene, R.sup.4 .dbd.R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 .dbd.4--ClC.sub.6 H.sub.4)

DETD i. (1S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-[5-(aminocarbonyl)benzoxazol-2-yl]hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula III, heterocycle containing X, N and Q.dbd.5-(aminocarbonyl)benzoxazol-2-yl, A.dbd.CO, L.dbd.p-phenylene, R.sup.4 .dbd.R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 .dbd.4--ClC.sub.6 H.sub.4)

DETD j. (S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-[5-(aminocarbonyl)benzoxazol-2-yl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q.dbd.5-(aminocarbonyl)benzoxazol-2-yl, A.dbd.CO, L.dbd.p-phenylene, R.sup.4 .dbd.R.sup.5.S(O.sub.2).NH.CO--, R.sup.5 .dbd.4--ClC.sub.6 H.sub.4)

CLM What is claimed is:

9. A compound as claimed in claim 1 selected from a group consisting of: (i) [4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-(5-hydroxybenzoxazol-2-yl)carbonyl-2-methylpropyl]-L-prolinamide; (ii) [4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-[5-(aminocarbonyl)benzoxazol-2-yl)carbonyl-2-methylpropyl]-L-prolinamide; (iii) [4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoyl]-L-valyl-N-[1-[5-(hydroxymethyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide; and pharmaceutically acceptable base-addition salts thereof.

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AB The invention concerns pharmaceutically useful trifluoromethyl ketone substituted di-, tri- and tetra-peptide derivatives of the formulae Ia, Ib, Ic set out hereinafter, and salts thereof, which are inhibitors of human leukocyte elastase. Also described herein are pharmaceutical compositions containing a peptide derivative and processes and intermediates for use in the manufacture of the peptide derivatives.

PI US 5055450 19911008 <--

SUMM . . . in pharmacological, diagnostic and related studies and in the treatment of tissue degenerative diseases such as pulmonary emphysema, atherosclerosis, rheumatoid **arthritis** and osteo **arthritis** in warm blooded animals. The invention also includes

intermediates useful in the synthesis of these peptide derivatives, processes for preparing. . .

SUMM (x) acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsufonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . by a member selected from carboxy, alkoxycarbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . .

SUMM . . . a member selected from carboxy, alkoxycarbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . .

SUMM (x) acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons), and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . 6 carbons), alkoxy carbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing from 1 to 15 carbons, and provided that when the acylsulfonamido contains an aryl the aryl may be further. . .

SUMM . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons (e.g., 4-[(4-chlorophenyl) -**sulfonylaminocarbonyl**]phenyl or 4-[(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl);

SUMM (x) ethyl substituted by an acylsulfonamido selected from the group consisting of 2-(methylsulfonylaminocarbonyl)ethyl, 2-(phenylsulfonylaminocarbonyl)ethyl, 2-[(I -adamantyl) **sulfonylaminocarbonyl**]ethyl, and 2-[(1-naphthyl) **sulfonylaminocarbonyl**]ethyl;

SUMM . . . carboxy, methoxy, ethoxy, methoxycarbonyl, ethoxycarbonyl, methylcarbonylamino, an acylsulfonamido containing 2 carbons, (e.g., 4-(methylsulfonaminocarbonyl)phenyl), an acylsulfonamido containing 7 carbons (e.g., 4-(phenylsulfonylaminocarbonyl)phenyl, 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl, or [(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl), an acylsulfonamido containing 11 carbons (e.g., 4(1-naphthylsulfonylaminocarbonylphenyl), an acylsulfonamido containing 14 carbons (e.g., 4-(4-bromophenylsulfonylamino(benzyl)carbonyl)phenyl); and an aryl group containing 6. . .

SUMM (X) an ethenyl group substituted by a member selected from the group consisting of carboxy, ethoxycarbonyl, ureidocarbonyl (e.g., Z-2-(aminocarbonylamino)ethenyl)), acylsulfonamidophenyl (e.g.,2-[4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl]-ethenyl), and 4-carboxyphenyl (e.g., E-2-(4-carboxyphenyl)ethenyl;

SUMM . . . to a warm-blooded animal in need thereof, particularly a human, for the treatment of conditions of pulmonary emphysema, atherosclerosis, rheumatoid **arthritis**, and osteo **arthritis**, in particular for emphysema. The mode of administration may be oral, parenteral, including the subcutaneous deposit by means of an. . .

DETD 3(RS)-4-[(4-Nitrophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-NO.sub.2 .phi.)S(O.sub.2)NHCO].phi., R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Br.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD b. 3(RS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Br-.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1).

DETD 3(RS)-[3-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl]-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi.(CH.sub.2).sub.2, R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-E-[3-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl]-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =E-[4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi.--CH.dbd.CH--, R.sup.4 =H, A=CO, n=1)

DETD 3S(or R)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 4-[(4-Br.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD 3R(or S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl]carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =CH(CH.sub.3)CH.sub.3, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHCO].phi., R.sup.4 H, A=CO, n=1)

DETD a. 1,1-Dimethylethyl 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**

]benzoate.

DETD b. 4-[4-Chlorophenyl)**sulfonylaminocarbonyl**]benzenecarboxylic acid.

DETD c. 2(RS),3(SR)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide

DETD d. 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =CH(CH.sub.3)CH.sub.3, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHCO].phi., R.sup.4 =H, A=CO, n=1).

CLM What is claimed is:

. . . to 13 carbons; (w) arylsulfonamido wherein the aryl group contains 6, 10 or 12 carbons; (x) acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal portion of the acylsulfonamide. . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . . by a member selected from carboxy, alkxoycarbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . . a member selected from carboxy, alkoxycarbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . . to 13 carbons; (w) arylsulfonamido wherein the aryl group contains 6, 10 or 12 carbons; (x) acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazol, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 5 carbons), and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . . to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acrylsulfonamido contains an aryl the aryl may be further substituted by. . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . . to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing from 1 to 15 carbons, and provided that when the acrylsulfonamido contains an aryl the aryl may be further. . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

. . . the aryl portion contains 6 carbons; (x) ethyl substituted by an acylsulfonamido selected from the group consisting of 2-(methylsulfonylaminocarbonyl)ethyl, 2-(phenylsulfonylaminocarbonyl),

2-[(1-adamantyl)**sulfonylaminocarbonyl**]ethyl, and 2-[(1-naphthyl)**sulfonylaminocarbonyl**]ethyl; (y) an alkyl group containing 2 or 10 carbons and substituted by methoxycarbonyl; (z) an alkyl group containing 2 to. . .

. . . to 13 carbons; (w) arylsulfonamido wherein the aryl group contains 6, 10 or 12 carbons; (x) acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal portion of the acylsulfonamide. . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsufonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl may be further substituted by a member. . .

7. A compound of formula VIIb ##STR10## wherein: R.sup.1 is isopropyl; R.sup.2 is isopropyl; R.sup.3 is 4-[1-naphthylsulfonyl)aminocarbonyl]phenyl, 4-[(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl, or 4-[4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl; R.sup.4 is hydrogen; n=1; and A is ##STR11## or a base addition salt thereof.

L2 ANSWER 18 OF 21 USPATFULL on STN

AB The invention relates to selected difluoro compounds of formulae Ia, Ib and Ic (set out hereinafter) which are useful as inhibitors of human leukocyte elastase.

PI US 4923890 19900508 <--

SUMM . . . tools in pharmacological and related studies and in the treatment of tissue degenerative diseases such as pulmonary emphysema, atherosclerosis, rheumatoid **arthritis** and osteoarthritis in warm blooded animals. The invention also includes intermediates useful in the synthesis of these peptide derivatives, processes. . .

SUMM (x) acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons), alkanoyloxy (2 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsufonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or 12. . .

SUMM . . . by a member selected from carboxy, alkoxycarbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 2 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or. . .

SUMM . . . a member selected from carboxy, alkoxycarbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 2 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or. . .

SUMM (x) acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons), and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or 12. . .

SUMM . . . to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, acylsulfonamido (i.e. acylaminosulfonyl and

sulfonylaminocarbonyl) (2 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or 12. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing from 2 to 15 carbons, and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10. . .

SUMM . . . group consisting of carboxy, alkoxycarbonyl wherein the alkoxy group contains 1 to 4 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons), alkanoyloxy (2 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or 12. . .

SUMM . . . to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or 12. . .

SUMM . . . by a member selected from carboxy, alkoxycarbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 2 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or. . .

SUMM . . . a member selected from carboxy, alkoxycarbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 2 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons), and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or 12. . .

SUMM . . . to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or 12. . .

SUMM . . . group consisting of carboxy, alkoxycarbonyl wherein the alkoxy group contains 1 to 4 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 2 to 15 carbons (e.g., 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl or 4-[(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl);

SUMM . . . to a warm-blooded animal in need thereof, particularly a human,

for the treatment of conditions of pulmonary emphysema, atherosclerosis, rheumatoid **arthritis**, and osteo **arthritis**, but in particular for emphysema. The mode of administration may be oral, parenteral, including the subcutaneous deposit by means of. . .

L2 ANSWER 19 OF 21 USPATFULL on STN

AB The invention concerns pharmaceutically useful trifluoromethyl ketone substituted di-, tri- and tetra-peptide derivatives of the formulae Ia, Ib, Ic set out hereinafter, and salts thereof, which are inhibitors of human leukocyte elastase. Also described herein are pharmaceutical compositions containing a peptide derivative and processes and intermediates for use in the manufacture of the peptide derivatives.

PI US 4910190 19900320 <--

SUMM . . . in pharmacological, diagnostic and related studies and in the treatment of tissue degenerative diseases such as pulmonary emphysema, atherosclerosis, rheumatoid **arthritis** and osteo **arthritis** in warm blooded animals. The invention also includes intermediates useful in the synthesis of these peptide derivatives, processes for preparing. . .

DETD (x) acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

DETD . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsufonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

DETD . . . by a member selected from carboxy, alkoxycarbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . .

DETD . . . a member selected from carboxy, alkoxycarbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 1 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted. . .

DETD (x) acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

DETD . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons), and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

DETD . . . to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

DETD . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

DETD . . . to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e.,

acylaminosulfonyl and **sulfonylaminocarbonyl**) containing from 1 to 15 carbons, and provided that when the acylsulfonamido contains an aryl the aryl may be further. . .

DETD . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

DETD . . . alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons (e.g., 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl or 4-[(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl);

DETD (x) ethyl substituted by an acylsulfonamido selected from the group consisting of 2-(methylsulfonylaminocarbonyl)ethyl, 2-(phenylsulfonylaminocarbonyl)ethyl, 2-[(1-adamantyl)**sulfonylaminocarbonyl**]ethyl, and 2-[(1-naphthyl)**sulfonylaminocarbonyl**]ethyl;

DETD . . . carboxy, methoxy, ethoxy, methoxycarbonyl, ethoxycarbonyl, methylcarbonylamino, an acylsulfonamido containing 2 carbons, (e.g., 4-(methylsulfonaminocarbonyl)phenyl), an acylsulfonamido containing 7 carbons (e.g., 4-(phenylsulfonylaminocarbonyl)phenyl, 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl, or [(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl), an acylsulfonamido containing 11 carbons (e.g., 4(1-naphthylsulfonylaminocarbonylphenyl), an acylsulfonamido containing 14 carbons (e.g., 4-(4-bromophenylsulfonylamino(benzyl)carbonyl)phenyl); and an aryl group containing 6. . .

DETD . . . an ethenyl group substituted by a member selected from the group consisting of carboxy, ethoxycarbonyl, ureidocarbonyl (e.g., Z-2-(aminocarbonylamino)ethenyl)), acylsulfonamidophenyl (e.g., 2-[4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl]ethenyl), and 4-carboxyphenyl (e.g., E-2-(4-carboxyphenyl)ethenyl;

DETD . . . to a warm-blooded animal in need thereof, particularly a human, for the treatment of conditions of pulmonary emphysema, atherosclerosis, rheumatoid **arthritis**, and osteo **arthritis**, in particular for emphysema. The mode of administration may be oral, parenteral, including the subcutaneous deposit by means of an. . .

DETD 3(RS)-4-[(4-Nitrophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH-, R.sup.3 =4-[(4-NO.sub.2 .phi.)S(O.sub.2)NHCO].phi., R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH-, R.sup.3 =4-[(4-Br.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD b. 3(RS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]-phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH-, R.sup.3 =4-[(4-Br-.phi.)S(O.sub.2) NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi.--, R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-[3-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl]-1-oxopropyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi.(CH.sub.2).sub.2, R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-E-[3-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl]-1-oxoprop-2-enyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =E-[4-[(4-Cl.phi.)S-(O.sub.2)NHC(O)].phi.-CH=CH--, R.sup.4 =H, A=CO, n=1)

DETD 3R(orS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxo-pentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[4-(Br.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD 3S(or R)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Br.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD 3S(or R)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD 3R(or S)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenyl]carbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =(CH.sub.3).sub.2 CH--, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHC(O)].phi., R.sup.4 =H, A=CO, n=1)

DETD 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =CH(CH.sub.3)CH.sub.3, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHCO].phi., R.sup.4 =H, A=CO, n=1)

DETD a. 1,1-Dimethylethyl 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoate

DETD b. 4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzenecarboxylic acid

DETD c. 2(RS),3(SR)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-2-hydroxy-4-methylpentyl)]-L-prolinamide (Formula VIIb, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =CH(CH.sub.3)CH.sub.3, R.sup.3 =4-[(4Cl-.phi.)S(O.sub.2)NHCO].phi., R.sup.4 =H, A=CO, n=1)

DETD d. 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide (Formula Ib, R.sup.1 =CH(CH.sub.3)CH.sub.3, R.sup.2 =CH(CH.sub.3)CH.sub.3, R.sup.3 =4-[(4-Cl.phi.)S(O.sub.2)NHCO].phi., R.sup.4 =H, A=CO, n=1)

CLM What is claimed is:

. . . to 13 carbons; (w) arylsulfonamido wherein the aryl group contains 6, 10 or 12 carbons; (x) acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal portion of the acylsulfonamide. . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsufonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (1 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . . . 12 carbons; R.sup.3 is an aryl group containing 6, 10 or 12 carbons suitably substituted by acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing from 1 to 15 carbons, and provided that when the acylsulfonamido contains an aryl the aryl may be further. . .

. . . A compound as claimed in claim 1 selected from the group consisting of: (a) 3(RS)-[4-(Methylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; (b)

3(RS)-[4-(Phenylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; (c) 3(RS)-[[4-[(1-Naphthylsulfonyl)aminocarbonyl]phenyl]aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; (d) 3(RS)-4-[(4-Nitrophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; (e) 3(RS)-[4-(Phenylsulfonylaminocarbonyl)phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; (f) 3(RS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; (g) 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; (h) 3S(or R)-[4-(Phenylsulfonylaminocarbonyl)phenylaminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; (i) 3S(or R)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; and (j) 3S(or R)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide.

5. A compound as claimed in claim 5 selected from the group consisting of: (1) 3(RS)-[[4-[(1-Naphthylsulfonyl)aminocarbonyl]phenyl]aminocarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; (2) 3(RS)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; (3) 3(RS)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; (4) 3S(or R)-[4-[(4-Bromophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide; and (5) 3S(or R)-[4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide.

L2 ANSWER 20 OF 21 USPATFULL on STN

AB The invention discloses a series of difluoroketone, mono- di- and tri-peptide derivatives of formula Ia, Ib and Ic:

(Formula set out on pages following Examples)
Ia
(Formula set out on pages following Examples)
Ib
(Formula set out on pages following Examples)
Ic

and salts thereof where appropriate, and wherein the radicals are defined hereafter in the specification. The derivatives are useful in inhibiting the action of human leukocyte elastase. There are also disclosed methods and intermediates for the manufacture of, and pharmaceutical compositions comprising, the said derivatives.

PI US 4880780 19891114 <--

SUMM . . . tools in pharmacological and related studies and in the treatment of tissue degenerative diseases such as pulmonary emphysema, atherosclerosis, rheumatoid **arthritis** and osteoarthritis in warm blooded animals. The invention also includes intermediates useful in the synthesis of these peptide derivatives, processes. . .

SUMM (x) acylsulfonamideo (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) including

acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons), alkylcarbonyloxy (2 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or 12. . .

SUMM . . . by a member selected from carboxy, alkoxycarbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 2 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or. . .

SUMM . . . a member selected from carboxy, alkoxycarbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 2 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or. . .

SUMM (x) acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons), and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or 12. . .

SUMM . . . (2 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, acylsulfonamido (i.e., acylaminosulfonyland **sulfonylaminocarbonyl**) (2 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or 12. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) containing from 2 to 15 carbons, and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10. . .

SUMM . . . group consisting of carboxy, alkoxycarbonyl wherein the alkoxy group contains 1 to 4 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons), alkanoyloxy (2 to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or 12. . .

SUMM . . . to 6 carbons), alkoxy (1 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by. . .

SUMM . . . alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 2 to 15

carbons (e.g., 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl or 4-[(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl);

SUMM . . . to a warm-blooded animal in need thereof, particularly a human, for the treatment of conditions of pulmonary emphysema, atherosclerosis, rheumatoid **arthritis**, and osteo **arthritis**, but in particular for emphysema. The mode of administration may be oral, parenteral, including the subcutaneous deposit by means of. . .

DETD c. 1,1-Dimethylethyl 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]benzoate

DETD d. 4-[(4-Chlorophenyl)**sulfonylaminocarbonyl**]benzoic acid

L2 ANSWER 21 OF 21 USPATFULL on STN

AB The invention relates to selected difluoro compounds of formulae Ia, Ib and Ic (set out hereinafter) which are useful as inhibitors of human leukocyte elastase.

PI US 4873221 19891010 <--

SUMM . . . tools in pharmacological and related studies and in the treatment of tissue degenerative diseases such as pulmonary emphysema, atherosclerosis, rheuma-toid **arthritis** and osteoarthritis in warm blooded animals. The invention also includes intermediates useful in the synthesis of these peptide derivatives, processes. . .

SUMM (x) acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons), alkanoyloxy (2 to 6 carbons), alkoxycarbonyl (1 to 6 carbons), carboxy, 5-tetrazolo, and acylsufonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or 12. . .

SUMM . . . by a member selected from carboxy, alkoxycarbonyl, where alkoxy is 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 2 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or. . .

SUMM . . . a member selected from carboxy, alkoxycarbonyl, where the alkoxy has 1 to 3 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing 2 to 15 carbons and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or. . .

SUMM (x) acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons), and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or 12. . .

SUMM . . . to 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) and provided that when the acylsulfonylamido contains an aryl the aryl contains 6, 10 or 12. . .

SUMM . . . 6 carbons), alkoxycarbonyl (2 to 6 carbons), carboxy, aminocarbonylalkyl (2 to 6 carbons), aminocarbonyl, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) containing from 2 to 15 carbons, and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10. . .

SUMM . . . group consisting of carboxy, alkoxycarbonyl wherein the alkoxy group contains 1 to 4 carbons, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) including acylsulfonamido wherein the acyl group contains 1 to 7 carbons when it is the terminal. . .

SUMM . . . to 6 carbons), alkanoyloxy (2 to 6 carbons), alkoxycarbonyl (2 to 6 carbons) carboxy, 5-tetrazolo, and acylsulfonamido (i.e. acylaminosulfonyl and **sulfonylaminocarbonyl**) (2 to 15 carbons) and provided that when the acylsulfonamido contains an aryl the aryl contains 6, 10 or 12. . .

SUMM . . . alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 2 to 15 carbons (e.g., 4-[(4-chlorophenyl)**sulfonylaminocarbonyl**]phenyl or 4-[(4-bromophenyl)**sulfonylaminocarbonyl**]phenyl);

SUMM . . . to a warm-blooded animal in need thereof, particularly a human, for the treatment of conditions of pulmonary emphysema, atherosclerosis, rheumatoid **arthritis**, and osteo **arthritis**, but in particular for emphysema. The mode of administration may be oral, parenteral, including the subcutaneous deposit by means of. . .